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PRELIMINARY REPORT
ON THE TREATMENT OF
PULMONARY TUBERCULOSIS
WITH TUBERCULIN

NOEL D. BARDSWELL

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PRELIMINARY REPORT
ON THE
TREATMENT OF PULMONARY
TUBERCULOSIS WITH TUBERCULIN



King Edward VII Sanatorium, Midhurst

PRELIMINARY REPORT

ON THE

TREATMENT OF PULMONARY
TUBERCULOSIS WITH TUBERCULIN

BY

NOEL D. BARDSWELL, M.D.

MEDICAL SUPERINTENDENT

WITH A

PREFATORY NOTE

BY

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DIRECTOR OF THE GALTON LABORATORY OF EUGENICS,
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to the Council, and published at the
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PREFATORY NOTE

BY

PROFESSOR KARL PEARSON, F.R.S.

(1) IN December 1913 Dr. W. Bulloch placed before me, at the desire of the Consulting Staff of the King Edward VII Sanatorium, the statistical data involved in Sections XVI, XVII, and XVIII of Dr. Bardswell's Report, with a request that I would express an opinion on the conclusions with regard to the use of tuberculin which could be drawn statistically from this material. I at once saw that without further information it would be impossible to express any opinion, because the whole problem turned on the nature of the selection made of patients for tuberculin treatment. This additional information was at once placed in my hands by Dr. Bardswell, and it was obvious by aid of it that the problem was a very complex one, involving a long series of characteristics of the individual patients, divergent periods and methods of treatment, and criteria of improvement which could not be reduced to a single factor, such as absence of T.B. in the sputum on the last examination before discharge. It meant three or four months' work in careful analysis and reduction before a real judgment could be made, even if the material were not too slender at present to admit of a definite judgment at all. I promised to undertake this, but at the same time I made an interim report stating the grounds why it appeared to me unsafe to draw any conclusions from the data provided. This interim report was only intended for

the private use of the Consulting Staff, but at the express desire of Sir James K. Fowler and with Dr. Bardswell's approval, I have permitted my notes on the statistical data of the Report to be printed here. There is so much else of high value in Dr. Bardswell's memoir, that it would be undesirable to delay its publication until a detailed treatment of the statistical sections is forthcoming. On the other hand, it may be of service to record some of the reasons why at least one statistician cannot see in certain percentages which apparently tell somewhat in favour of tuberculin treatment any security for its value, until correction has been made for a long series of modifying factors. The following paragraphs give my original notes on the statistical data.

(2) I have found grave difficulty in dealing rapidly with the problem placed before me. It is not only that there are many statistical pitfalls, which must be unearthed and avoided, but further, that the complete analysis must be a labour of several months when the requisite additional data have been provided.

There is no doubt in my own mind that the most satisfactory method of dealing with the relative merits of various forms of treatment is to test the survival rate for each year after treatment of each differentiated group of patients. This is the method adopted by Mr. Palin Elderton in his investigations into the mortality of the tuberculous. It involves keeping in touch each year with the patients discharged in various previous years. Dr. Laurason Brown in America, Dr. Fanning and Dr. Bardswell himself in this country among others have shown the possibility of achieving this with a relatively small leakage of "lost sight of," if due precautions are taken and yearly inquiries made. There is no reason for supposing that for the same class of patient there will be any differentiation of environment after treatment, which would be associated with treatment in a

particular manner. Further, the information obtained in three to five years is sufficient to test relative survival rates.¹

Dr. Bardswell's inquiry would hasten a decision on the efficiency of tuberculin by determining whether the tubercle bacillus has disappeared in a greater number of cases on discharge in the case of pure sanatorium treatment or of such treatment combined with tuberculin. This seems *a priori* a most hopeful method of attacking the problem, but we soon find that it leads statistically to great complexities of analysis.

I have been unable to convince myself—I speak as a layman—that we have at present an adequate measure of the real loss of T.B. in the mere record of the last sputum examination before discharge. For example, take a record of the fortnightly examinations of the following kind :

+ + + - + + - + -

This patient was, no doubt, better when discharged, the T.B. in the latter part of his stay in the sanatorium is less frequently recorded. But are we to reckon him as a "T.B. lost," when a fortnight earlier, if he had taken his discharge, T.B. would still have been found? But this again would be an unfair verdict, because he has undoubtedly improved; he has more minus signs in the latter half of his stay. *After much consideration it appears to me that the absence or presence of T.B. as a test of condition can only be satisfactory if it does not refer merely to the last examination, but due weight be given to*

¹ I was consulted some years ago by a medical man setting up a Tuberculin dispensary as to the best method of collecting data to test the efficiency of the treatment. On my replying that it was summed up in following the treated for four or five years, he seemed grievously disappointed. However, within a year he felt able to publish one, if not two, papers demonstrating on other than actuarial grounds the value of tuberculin!

every sputum examination in relation to the length of time in the sanatorium, and to the length of time under tuberculin treatment. I do not think any other method of dealing with the sputum test will be satisfactory, and I believe a process can be devised for carrying this out ; but it is lengthy, and involves reductions for each individual which require considerable labour and time.

In other words, I should propose to replace the mere judgment "lost T.B.," which covers three such diverse cases as (a), (b), and (c) below, by a graduated measure of the extent or degree to which T.B. has disappeared under treatment.

(a) + + + - + - - - -
(b) - + -
(c) + + + - + + - + -

I do not think we ought to classify as belonging to the same category such cases as the above ; (a) is so obviously better than (c), and of (a) and (c) we have far greater experience than of (b), so that our observations must be weighted as well as graduated. With a method such as I suggest, I think, we should be able to determine whether the prevalence of T.B. in the sputum is or is not reduced more by tuberculin and sanatorium treatment, or by the sanatorium treatment alone.

It should be the object of a further inquiry to ascertain whether this reduced prevalence on discharge, if it exists, is markedly associated with a greater survival rate after leaving the sanatorium. *A priori* we should anticipate that it would be,¹ but it would, I think, be desirable not to dogmatise on this point until survival data are forthcoming.

(3) The next all-important factor in the inquiry is the

¹ Of 158 patients treated in the Sanatorium from 1906 to 1911 who lost their bacilli, 84% were well and alive in 1911, 16% were dead. Whereas of 606 patients treated during the same period who did not

marked selection of patients for tuberculin treatment. They are very far from a random sample of the sanatorium population. It is well known that tuberculin is only considered suitable for those patients who still possess considerable constitutional vigour and powers of recuperation. Afebrile cases and those showing but slight signs of constitutional deterioration appear to be usually selected. Now this renders comparison with non-tuberculin cases—not impossible, but distinctly difficult. We are bound to equalise the *initial* states of the patients before treatment. Regard must be paid to age, which has not been considered in Sections XVII and XVIII. Then we must take into account measures of physical deterioration on admission, and of these weight for age and for stature and again temperature-range appear the most promising. Beyond these we have the Turban grouping as a measure of the progress of the disease before treatment. This in its very nature offers some difficulty ; there are always borderland cases, and the percentage of these borderland cases may be markedly altered if there be selection on admission to the sanatorium or in administration of tuberculin. There is no doubt in my own mind that in recent years the milder cases have been more and more selected for sanatorium treatment. This does not only mean that we get more cases relatively of Group I and fewer of Group III, but that the average severity in each group has been reduced. Thus comparison between the same groups in different years is not necessarily a comparison of equally severe cases. It is more than conceivable

lose their bacilli, 50% were well or alive in 1911 and 50% were dead. This at first looks a complete answer to the question, but the problem is far more complex. The average conditions of the 158 and 606 groups of patients were scarcely the same when they reached the sanatorium either as to age, general health, or Turban class. If we are to measure the different treatments by loss of T.B. and the effect of this on later survival rates, we must equalise our patients' condition *ab initio*.

that if we confined our attention, say to Group II, we should not find the tuberculin and non-tuberculin patients equalised groups. The former, with the selection we know takes place of afebrile and more favourable cases, would provide in all probability a larger proportion of the cases bordering on Group I. The like remark applies to Group I, where indeed it is probably idle to consider the question of tuberculin at all. It appears to be admitted that most of these patients do remarkably well under sanatorium treatment alone, and accordingly it becomes rather a question of whether tuberculin tends to accelerate or retard their progress. This probably cannot be wholly settled by the question of T.B. in the sputum, as their physical condition—as measured by their capacity for exertion—may be of almost equal importance. Group III also may be largely left out of account, as the chief supporters of tuberculin hardly assert that it produces much favourable effect in this class of case.

Some further difficulty may arise also from the introduction of more accurate methods of testing for T.B. But I do not at present anticipate much trouble from the occasional use of the E. and E. test,¹ *provided* the condition be determined, not by the *last* sputum test, but on the basis of all tests made during the stay in the sanatorium.

It will be obvious that if it be needful to suspend our judgment until correction has been made for the points referred to, it will be needful to add much more information than is provided in Sections XVII and XVIII. Dr. Bardswell has expressed his willingness to provide this, and already has given me additional data. I hope to more fully analyse these factors later. At present I would only press on the reader the need for no dogmatic conclusions.

¹ See page 2.

(4) With regard to the wording of the XVIIth and XVIIIth sections, it appears to be very cautious and on the whole non-committal. But I think that the main results as cited in the Table, p. 84, will not permit conclusions to be drawn from them until (as Dr. Bardswell himself suggests, pp. 88 and 132) they have received actuarial treatment, including the corrections I have just referred to as those for age, physical condition at admission, length of treatment with and without tuberculin, etc. Without allowance for these factors, I do not feel satisfied, to quote Dr. Bardswell's own words, that he is really placing "the facts before the reader of this report," and "allowing him to draw his own conclusions" (p. 89). It is not easy to see all round facts, much less percentages; they are generally very many-sided, and in the present case they might be very much modified by correction for the numerous factors involved, but not discussed.

As an illustration of my meaning, let me take the rise in the percentage of cases with "T.B. lost" in Group I in 1910-11 and 1911-12. In 1910-11 27.7% of the patients in this group, *all without tuberculin*, lost T.B. In 1911-12 this percentage rose to 47.5% with a shorter time in the sanatorium. Here is a fact which looks like an immense increase in the percentage of "T.B. lost" owing to the introduction of tuberculin treatment! But now let us see another side of the "fact." If we divide up the patients of Group I in 1911-12 into the 31 treated *without tuberculin* and the 9 *with tuberculin*, we find that those without have risen on discharge to 48.4% with "T.B. lost," and those with have risen only to 44.4%. In other words, in this group the betterment is rather higher—if we could trust such slender numbers—for those without than for those with the tuberculin treatment. The betterment in Group I is not due, therefore, to the introduction of tuberculin treatment, but to some other cause which affected both

classes of patients. It may be due to a more stringent selection for admission, to better weather conditions, or to some general change of treatment, which no doubt a thorough analysis of the data would bring to light.

Again in Group II, 1911-12, there is not improvement on Group II, 1908-9, although in 1911-12 the tuberculin section do better than the non-tuberculin section. In 1908-9 certainly the tests for admission were less stringent, and the general condition of Group II was likely to be lower. In Group III the two cases who lost T.B. during sanatorium treatment both came in 1911-12 from the non-tuberculin group, but then only one case in this group was treated with tuberculin. It will be thus clear that the whole discussion must practically turn on what happened to the patients in Group II. If we could say that Group II was the same in 1908-9 and 1911-12 and the test for "T.B. lost" was as perfect, then tuberculin treatment would have achieved nothing between those years, for 19.3-19.4% lost T.B. in *both*. But as a matter of fact we cannot hazard a judgment until we have demonstrated by reference to ages, physical conditions, length of stay in sanatorium, etc., that the persons in these two Groups II were really alike.

I have not the data at present needful for doing this, but I can point out from Group II in the following year how needful it is to undertake it. For this Group II in 1912-13 we can hardly discuss the general point, because 80% of the patients who fall into it were tuberculin treated; but it suffices to note that of the non-tuberculin group no less than 52.4% were in unfavourable general health on admission, while only 26.4% of those subject to tuberculin treatment were in a similar condition. In other words, the tuberculin group came to the sanatorium in twice as favourable a condition of health, and on that account alone we should anticipate that they would be twice as likely to profit by their stay. On grounds such

as these, I think, the reader should be warned not to take the results on pp. 84 and 88 at their face values. Dr. Bardswell has indeed given the warning that the reader should suspend his judgment, but I think, as the table on p. 84 is likely to be quoted by partisan writers for far more than it is really worth, an additional emphasis by way of the above illustrations may not be amiss.

In conclusion, let me observe that the statistical data do not show that obvious and marked advantage of tuberculin treatment which would raise it at once above all suspicion of showing what advantage it does show owing to selection of patients. Correction for selection may show it with a slight credit or an actual debit. In the face of such possibilities, is not the right attitude that which considers it as a treatment very much in the experimental stage, and when such an attitude is taken, are we not ethically justified in dealing with it in the only judicious *experimental* manner? We cannot tell a patient with any certitude that it will benefit him, and we are not bound, therefore, to apply it. On the other hand, we cannot definitely say at present that with selected classes of patients, cautiously treated, it is positively detrimental. If it were possible the scientific method would be to select patients suitable for tuberculin treatment, treat only those whose surnames began with A to K, and then compare the results with simple sanatorium treatment of the remainder, L to Z, of these selected patients. Thus in two or three years we should know exactly the value of the treatment. When all selected cases are treated as at present, we shall have no suitable control to determine whether the treatment has any real value, unless indeed we again leave it off.

CONTENTS

	PAGE
Prefatory Note
Introduction
 SECTION I 	
The Physical Examination of Patients
(a) <i>Examination of Sputum</i>
(b) <i>Selection of Cases</i>
 SECTION II 	
Tuberculin
(a) <i>Variety of Tuberculin Used</i>
(b) <i>Site of Inoculation and Method of Administration</i>
 SECTION III 	
Treatment by Tuberculin
<i>Methods and Objects</i>
<i>Changes in the Lesions</i>
 SECTION IV 	
Dosage
1. <i>Measurement of Dose</i>
2. <i>The Initial Dose</i>
3. <i>Dilutions</i>
4. <i>Rate of Increase of Dose</i>
5. <i>Intervals between Doses</i>
6. <i>The Maximum Dose</i>
7. <i>Limit of Tolerance</i>
8. <i>Sensitiveness during Treatment</i>

SECTION V

	PAGE
Courses of Tuberculin Injection	20
<i>On 42 Cases in which injections of Tuberculin were not followed by Reactions</i>	<i>20</i>

SECTION VI

(a) Cases in which there was a Slight Response to Tuberculin short of an Objective Reaction	29
(b) Cases which show that the Absence of Reactions during a Course of Injections lasting for many months is not necessarily followed by demonstrable Benefit	30

SECTION VII

Cases in which Marked Reactions followed Injections of Tuberculin	34
------------------------------------------------------------------------------------	-----------

SECTION VIII

The Difficulty of Avoiding Reactions	44
(a) <i>Toxic Symptoms without Febrile Disturbance may indicate a Reaction</i>	<i>44</i>

SECTION IX

Tuberculin Injections in Febrile Cases	48
---------------------------------------------------------	-----------

SECTION X

Commentary on Tuberculin Injections in Relation to Reactions	50
-------------------------------------------------------------------------------	-----------

SECTION XI

Methods of Tuberculin Treatment now in Use at the Sanatorium	54
-------------------------------------------------------------------------------	-----------

CONTENTS

xvii

SECTION XII

	PAGE
The Effect of Tuberculin upon the Symptoms of Pulmonary Tuberculosis	56
1. <i>Cough and Sputum</i>	56
2. <i>Physical Signs</i>	56

SECTION XIII

Mixed Infections	61
-----------------------------------	-----------

SECTION XIV

Cases treated with Tuberculin after they had left Midhurst	62
<i>Reappearance of Tuberclle Bacilli in Sputum</i>	63
<i>The After-Histories of 42 Patients in whose Sputum Tuberclle Bacilli were not found when they left the Sanatorium</i>	65

SECTION XV

General Results in Cases Treated with Tuberculin in Addition to the Methods of Treatment usually carried out at the Sanatorium	67
<i>Method Adopted for Recording the Clinical Histories of Patients treated with Tuberculin</i>	67

SECTION XVI

General Results in 154 Cases treated with Tuberculin at Midhurst between October 1911 and May 1913	71
(a) <i>Records of 24 Cases in which Tuberclle Bacilli were not found in the Sputum</i>	71
(b) <i>Records of 130 Cases in which Tuberclle Bacilli were present in the Sputum</i>	73
(c) <i>The Fallacy of Selection of Cases</i>	74

SECTION XVII

	PAGE
A Comparison of Cases treated in the Sanatorium with and without Tuberculin	76
(a) <i>Comparison of General Results</i>	77
(b) <i>Comparison of Results as Estimated by the Disappearance or Non-disappearance of Tubercle Bacilli from the Sputum</i>	78

SECTION XVIII

Commentary on the Foregoing Statement of Results	79
-------------------------------------------------------------------	-----------

SECTION XIX

Observations on the Suggested Use of Tuberculin in Dispensaries and in General Practice throughout the Country	90
-----------------------------------------------------------------------------------------------------------------------------------------	-----------

SECTION XX

Records of Cases treated with Tuberculin in Private Practice and at Dispensaries and Elsewhere	92
---------------------------------------------------------------------------------------------------------------------	-----------

SECTION XXI

Summary of the Experience gained at Midhurst, up to October 1913, as to the Treatment of Pulmonary Tuberculosis with Tuberculin	132
----------------------------------------------------------------------------------------------------------------------------------------------------------	------------

Appendix I	135
Appendix II	136
Appendix III	137
Appendix IV	138
Appendix V	141

INTRODUCTION

TUBERCULIN has been employed to a limited extent in the Sanatorium for some years, but since 1911, its use has been materially increased. The publication, during the past few years, of reports in which the authors have claimed for tuberculin, definite value as a specific cure for pulmonary tuberculosis, has aroused the interest of the medical profession and the public in this subject. This interest has been reflected in a commonly expressed desire, on the part of patients and their medical advisers, that tuberculin should be given at the Sanatorium, in addition to the other means of treatment hitherto more exclusively employed. In the judgment of the Consulting Staff, the results claimed by those who advocate an extended use of tuberculin in the treatment of pulmonary tuberculosis justified the investigation as to the value of tuberculin, which the demand for this method of treatment made possible.

During the past two years, considerable experience has thus been gained in regard to the treatment of pulmonary tuberculosis with tuberculin, and some of the results obtained during the eighteen months following October 1, 1911, form the subject of this preliminary report. Greater prominence has perhaps been given to the less favourable results which have been noted, but at the present time there are good grounds for doing so.

The report may be regarded as a contribution to

INTRODUCTION

one of several aspects of the tuberculin problem, namely, the value of tuberculin as an addition to sanatorium treatment. They make it possible to give a partial answer to the question: "To what extent, if any, was the benefit to be derived from an average stay of six months in the sanatorium increased by the use of tuberculin as compared with a similar length of treatment in the same sanatorium when no tuberculin was given?"

Assuming this question to be answered, it is still a matter of opinion as to how far the answer will help in the solution of the larger problem, namely, the therapeutic value of tuberculin. The two are not identical. It is generally stated that in order to obtain the full advantage of the process of immunisation by tuberculin, inoculation should extend over a prolonged period, at least a year or more, so that the patient may undergo what is called "serial treatment," that is, a series of tuberculin courses, each of some months' duration, interrupted by intervals during which general treatment alone is given. It is for this reason that dispensaries and sanatoria working in connection (an arrangement which is extensively followed in Germany) may be expected to attain a greater measure of success than sanatoria working without such co-operation. So far as our work is concerned there has been no such co-operation, and, with but few exceptions, the patient's course of tuberculin has terminated with his discharge from the sanatorium.

To judge from our experience, the medical profession generally in this country is not as yet sufficiently versed in the details of the administration of tuberculin to warrant their undertaking this treatment with any confidence. As experience is gradually gained in the organisation

of dispensaries throughout the country, this difficulty may disappear. At present, therefore, treatment by tuberculin in sanatoria is open to the criticism that a large majority of the patients are not sufficiently long under observation, and that if success has been obtained, it is possible that such success would have been greater if the inoculations had been continued for a much longer period than the average of six months during which they remain in such institutions.

If, however, tuberculin is as powerful for good as some maintain, the adoption of tuberculin treatment by a sanatorium which hitherto has relied entirely upon general therapeutic measures should produce an appreciable effect upon the results. The average length of stay of patients in a sanatorium, though it may be too short to bring about the best results, is sufficiently long to allow of a very good estimate being formed as to the general effect of tuberculin. If tuberculin is retarding progress, the fact can be recognised in the course of a few weeks ; conversely, if it is doing good, indications should not be lacking of such benefit within the course of an average length of stay.

In a sanatorium, tuberculin is given under favourable conditions, the hygienic measures associated with sanatorium life being calculated to raise the general level of bodily health and thus to increase the chances of a satisfactory immunising response to inoculations. This fact to some extent compensates for the comparatively short period of treatment, and the results should at any rate be better than those which can be obtained by treating patients in the often unsatisfactory surroundings of their homes and work.



PRELIMINARY REPORT

ON THE

TREATMENT OF PULMONARY TUBERCULOSIS WITH TUBERCULIN

SECTION I

The Physical Examination of Patients

THE methods of clinical observation which have been in use since the opening of the sanatorium have proved sufficient for the control of patients treated with tuberculin.

The rectal temperature is taken on waking, also at 1 p.m. and 7 p.m., immediately after one hour's complete rest in the recumbent position.

The pulse rate is taken morning and evening on one day of the week, unless there are indications for more frequent observations.

The body weight is recorded every week.

The keeping of a continuous record of variations in temperature, weight, and amount of exercise prescribed, is to be commended, as in no other way can a general survey of the progress of a case be so well obtained. During a prolonged course of treatment, small fluctuations in weight and in the temperature, as, for example, a very gradual rise of the temperature to a higher level, are facts which may readily be overlooked, unless a continuous record is preserved.

An examination of the chest was at first made after every inoculation. Such frequent examinations, although

2 PRELIMINARY REPORT ON TUBERCULIN

possibly instructive, are not really necessary. As a working rule, it is found to be sufficient to examine the chest once a week, provided that an examination is also made whenever there is a rise of temperature or an increase of symptoms. It is safer, however, to err on the side of too frequent examinations than too few, for reactions at the seat of disease, although commonly associated with a rise of temperature and increase of symptoms, sometimes occur without any such indications, and may be overlooked, thus entailing the loss of information useful in the regulation of the treatment.

(a) Examination of Sputum

Should the ordinary film method give a negative result, examinations are made by the method of Ellerman and Erlandsen.¹

As a matter of routine, examinations are made once a month, but on the disappearance of bacilli, more frequent search is advisable.

(b) Selection of Cases

The endeavour has been to give tuberculin to all patients with the exception of those presenting definite contraindications ; and about 60% of all the cases admitted

¹ This so-called "Doppelmethode" is described by the authors in the *Zeitschrift für Hygiene*, etc., Band 61, s. 219, and is carried out as follows :

(1) One volume of sputum is mixed with half a volume of 0.6% sodium carbonate solution in a corked glass, and placed in the incubator at 37° C. for 24 hours.

(2) The greater part of the supernatant fluid is then poured off and the remainder is centrifuged.

(3) To the deposit so obtained, four volumes of 0.25% sodium hydrate solution are added, and after thorough mixing, the fluid is boiled.

(4) The resulting solution is again centrifuged.

(5) Films are made from the deposit obtained, and stained in the usual manner.

The above method has proved of great value, and is now used

to the sanatorium have thus been treated. The chief contra-indications are the existence of fever, marked constitutional debility, evidence of rapidly extending lesions, and indications of renal disease. A history of hæmoptysis has not been regarded as a contra-indication.

For the most part tuberculin has been given to those patients only who have reached a reasonable level of convalescence, as shown by absence of fever, a general sense of well-being, and ability to walk several miles daily without fatigue or rise of rest temperature taken at 1 and 7 p.m. It has been the invariable rule to keep every patient under observation for a time before beginning a course of tuberculin.

In addition to these afebrile cases, we have also treated a good many of a much less favourable type, that is, cases in which a course of complete rest and the usual sanatorium methods had failed to bring about sensible improvement.

exclusively in the sanatorium. It has the advantage over the anti-formin procedure in that (1) the reagents required are in common use and everywhere procurable, (2) there is no difficulty in getting the film to adhere to the slide, and (3) it may demonstrate the presence of tubercle bacilli where the other sedimentation processes fail.

SECTION II

Tuberculin

(a) Variety of Tuberculin Used

THE large number of tuberculin preparations now on the market are essentially identical in action. It is a question only of variation in strength, some varieties being more toxic, and thus more difficult to work with, than others. On general grounds, it would seem to be a good plan to give a course of extract tuberculin, such as Koch's old tuberculin, and to follow this with a course of endoplasm tuberculin containing insoluble fragments of the bacilli. During the first eighteen months of our work, we used almost exclusively two tuberculins, namely, Albu-mose Free Old Tuberculin (A.F.) and Koch's Bacillary Emulsion (B.E.). The former, prepared from tubercle bacilli grown upon a protein-free medium, is supposed to be less toxic than old tuberculin as grown according to Koch's original method.

Tuberculin made from bacilli of bovine strain is generally considered to be less toxic than that of human origin, and for this reason some prefer to give a preliminary course of bovine tuberculin. Since the beginning of the present year we have made an extended trial of this method, and have already satisfied ourselves that for purposes of administration bovine tuberculin is by no means as satisfactory as human tuberculin, even for the initial course. It is easier, indeed, to attain a reactionless course with A.F. than with the bovine preparations.

(b) Site of Inoculation and Method of Administration

The inoculations have all been made subcutaneously, for the most part in the fore-arm. With men, the loose tissue on the lower surface of the abdomen is a convenient site, as there is in this situation less tendency to induration and local reaction. The site of puncture is sterilised with tincture of iodine. Full antiseptic precautions are taken with the syringes and needles. It is a good plan, when making a number of inoculations, to keep the needles in boiling oil, as the points of needles thus sterilised are not blunted as they are when passed through a flame.

SECTION III

Treatment by Tuberculin

Methods and Objects

A BRIEF survey of the various methods of tuberculin administration may usefully precede a description of that adopted. Opinions vary greatly as to which method is both the safest and the most efficient, and this is not surprising, since we have no certain knowledge of the nature of the reaction to tuberculin, or of the processes which are set up by a tuberculin inoculation, or of the changes taking place in the diseased areas or elsewhere which give rise to the phenomena of a reaction.

Koch at first provoked marked reactions, hoping thereby to bring about sloughing and scarring of the area of disease. It was soon recognised, however, that marked reactions which could not be controlled entailed serious dangers, and the method fell into disuse.

As a result of much clinical and experimental evidence, it is now generally accepted that tuberculin treatment should aim at producing immunity to tuberculin, or at least at rendering the patient tolerant of considerable doses. Theoretically, by so doing, an immunity to tuberculosis should be created, carrying with it a lessened liability to relapse or extension of the disease. Further, it is believed that simultaneously with the process of progressive immunisation, fibrosis and ultimate healing of the diseased structures are promoted.

It has been found by clinical experience that tolerance or immunity to tuberculin is best promoted by the injec-

tions of gradually increasing doses. In this way a patient who at first reacts to a very small amount can in many cases be made tolerant of large doses. The constant repetition of a very small dose does not produce this tolerance ; indeed, by the frequent repetition of a dose of moderate amount, intolerance or hypersensitiveness, as the condition is usually termed, is actually encouraged.

Whether a high degree of tolerance to tuberculin is in itself of material advantage is a matter of opinion which cannot be determined until we know how far immunity to tuberculin means immunity to tuberculosis. On theoretical grounds, there should be some such advantage, and in practice the most favourable results which are claimed are associated with a disappearance of sensitivity to tuberculin.

The production of a high measure of tolerance is thus the aim of treatment, and when secured, it is regarded as evidence of a satisfactory response to tuberculin.

Changes in the Lesions

It is contended that to obtain the best results there must be some "stimulation"—to use this term quite empirically—of the focus of disease. Opinions vary as to the degree of "stimulation" that is desirable, but there is agreement that gradually increasing doses of tuberculin are necessary. The continued administration of small doses does not appear to cause any local stimulation in pulmonary cases, although it may do so in tuberculosis of other organs.

In 1907, some patients were treated at the sanatorium with small doses of tuberculin ; and although the fluctuations of the opsonic index were considered to indicate a satisfactory immunising response to the inoculations, there was no evidence of any effect, either favourable or unfavourable, upon the local lesion or upon the general

8 PRELIMINARY REPORT ON TUBERCULIN

condition. We certainly did not find any indication, symptomatic or objective, of focal stimulation, such as we have noticed since using the method of gradually increasing doses. The use of very small doses has the merit of being absolutely safe, but as they appear to have no effect, this form of reactionless treatment is no longer employed.

The slight reaction which, for want of a better term, I have expressed as "stimulation," and the grosser type of reaction, are probably only variations in degree of the same phenomenon.

The first is a reaction which often cannot be recognised, since it produces few symptoms or objective signs ; at the most, a transient and slight increase of sputum, or an equally transient and slight rise of temperature, may be observed. Clinically this is altogether different from the more pronounced effect, characterised by fever, malaise, and increase of symptoms. The term "reaction" has become limited to such objective signs ; but in practice there is every possible gradation from the imperceptible reaction to the most intense general and focal disturbance.

Some observers are of opinion that the production of a definite objective reaction amounts almost to mal-praxis, and they avoid all risk of such an eventuality by using very small initial doses, and by subsequently increasing the dose by minute amounts. The followers of this method, notably Sahli and Trudeau, claim that by it they can produce immunity to large doses of tuberculin, and secure for their patients all the advantages which tuberculin treatment is said to offer, without exposing them to the risks attendant on the production of marked reactions. This process of immunisation is necessarily a slow one, the time required for a single course of treatment being about fifteen months. This method is criticised on the ground that the security

against reactions is obtained at the sacrifice of the responses to tuberculin upon which successful immunisation depends. Yet this method of reactionless treatment might well be given an extensive trial at the sanatorium, as it is specially suitable for use in general practice and by those who are gaining their first experience of treatment by tuberculin.

Opposed to this "reactionless at all cost" school, there is another which sees in reactions little or no harm, and to a large extent ignores them. Petruschky, amongst others, holds this opinion.

The form of treatment which we have followed represents a compromise between these two extremes, in accordance with the methods given in detail by Bandelier and Roepke.¹

They term it "reactionless," though in practice their definition requires some modification. It would be more correct to say that reactions are objected to on principle, but are looked upon as unavoidable. It is not a reactionless method in the sense of Sahli; only relatively reactionless. As will be explained later, when discussing details of treatment, an absolutely reactionless course is the exception rather than the rule. So far, however, from ignoring reactions, this method recognises that they are a possible source of danger, since neither their intensity nor their duration can be controlled. Indications of their possible occurrence are carefully looked for, and by timely alteration of dose, and by other methods, efforts are sometimes successfully made to avoid them. To use a "sea-going" metaphor, the physician constantly sails very near the wind, and does so deliberately, hoping thereby to make certain of securing the desirable degree of reaction or stimulation. When this cautious method meets with mishap, in the shape

¹ Bandelier and Roepke, *Lehrbuch der spezifischen Diagnostik und Therapie der Tuberkulose* (Curt Kabitzsch, Würzburg, 1912).

10 PRELIMINARY REPORT ON TUBERCULIN

of a reaction, he utilises the experience to reshape his course, and by various means endeavours to escape similar accidents in the future. This is the attitude towards reactions professed by the greater number of those who use tuberculin. To judge, however, by their own reports, and by their charts recording the progress of cases, it is clear that there are wide diversities of view as to what constitutes a reaction, and of its gravity. Many would seem to take little heed of reactions even of fair degree, and of somewhat frequent occurrence ; that is, they do not consider them to contraindicate perseverance with the treatment of an individual patient. Others consider that no further evidence is required to condemn the treatment than the confession of inability to prevent the occurrence of reactions, or to control them when they occur.

The value of tuberculin as a means of treating pulmonary tuberculosis is thus closely bound up with this question of reactions, and every one who uses it has to make up his mind whether or not the provoking of reactions, or even the risk of provoking reactions, is desirable, barely justifiable, or absolutely unjustifiable. The decision at which he may arrive will determine his procedure.

SECTION IV

Dosage

(1) *Measurement of Dose*

THE dosage of tuberculin can be expressed in various ways. Some observers speak of doses in terms of milligrammes of the solid substance, others in terms of the original fluid, using the cubic centimetre as the standard. Others, again, adopt the cubic millimetre as the unit. For the purposes of comparison, I give the following table, for which I am indebted to the treatise on tuberculin treatment by Drs. Riviere and Morland.

Cubic Centimetre.	Cubic Millimetre.	Equivalent on older systems of measurement to :	
		A.F.	B.E.
c.c.	c.mm.	mgr.	mgr.
1	1,000	1,000	5
0.1	100	100	1/2
0.01	10	10	1/20
0.001	1	1	1/200
0.0001	0.1	1/10	1/2,000
0.00001	0.01	1/100	1/20,000
0.000001	0.001	1/1,000	1/200,000

(2) *The Initial Dose*

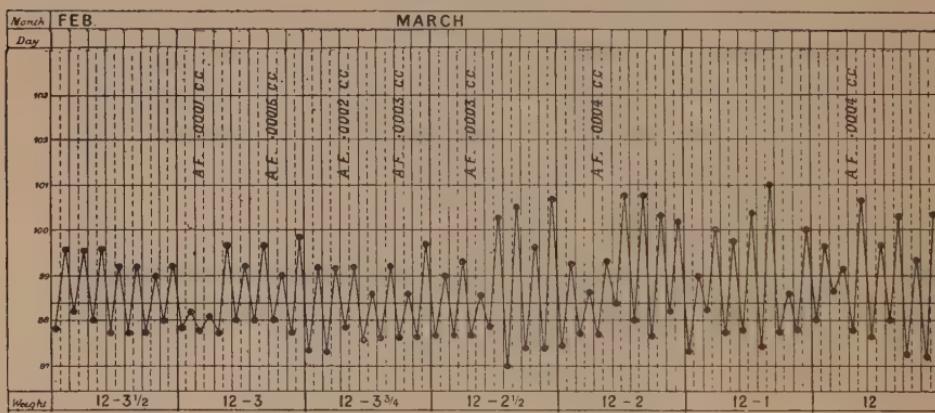
An initial dose of '00001 c.c. of A.F. or B.E. has proved to be suitable for patients who are afebrile and in good general condition. In some cases which showed a very considerable degree of arrest, and a high level of convalescence, '0001 c.c., as suggested by Bandelier and Roepke, has proved not to be too much. However, as there is

12 PRELIMINARY REPORT ON TUBERCULIN

nothing to be gained by this procedure, a larger initial dose than '00001 c.c. has rarely been used at Midhurst.

When there is fever or evidence of constitutional disturbance, a lower initial dose is indicated, namely, '000001 c.c. or '0000001 c.c.; otherwise the period of intolerance is reached comparatively early, and it becomes necessary to begin again with a smaller dose. An initial dose which proves to be too low is safer than one that is too high, and when in doubt, the lower of two possible doses is therefore to be preferred.

CHART 1.



The above chart shows the effect of an overdose, namely, loss of weight, a steadily rising temperature, and gradually increasing malaise, which necessitated the prescription of absolute rest.

(3) *Dilutions*

The usual dilutions for gradually increasing the doses were adopted, namely 1 in 10,000, 1 in 1,000, 1 in 100, and 1 in 10 of the original tuberculin solution. The dilution for the smallest dose was 1 in 100,000.

(4) *Rate of Increase of Dose*

The scale of dosage recommended by Bandelier and Roepke is by the series 1, 1·5, 2, 3, 5, 7, 10 for each dilution. We have modified this sequence from time to time, and on the whole find the series 1, 1·5, 2, 3, 4, 6, 8 to be more satisfactory.

There is an obvious convenience in having the various tuberculin dilutions prepared on the decimal system, each successive dilution being ten times stronger than the last ; and again in having syringes divided into ten equal parts for the measurement of the doses. By these means the measurement and recording of doses is a very simple matter. Thus, the record of '0001 c.c., '0003 c.c., '0005 c.c., etc., represents '1, '3, '5, etc., of a solution of 1 in 1,000, and so on throughout the dilutions.

Unfortunately, by this method the rate of increase of dose cannot be kept constant ; indeed, the increase of the strength of the dose may vary from 100% to 11%. To go from 1 to 2, for example, is to double the dose, hence the usual practice of inserting a dose of 1·5 between the two. This irregularity of the rate of increase of dose is a distinct disadvantage in the treatment of many of the less tolerant cases, and increases the difficulty of avoiding reactions. To remedy this, Pope, the statistician at the Adirondack Sanatorium, at the suggestion of Lawrason Brown, worked out a series of logarithmic scales of dosage, which, if followed, allows of the rate of increase of dose in any case remaining constant. Pope's scheme has twelve different scales of dosage, whereby, when going from '1 c.c. to 1 c.c. of any dilution, any number of doses may be given from a minimum of 2 to a maximum of 12. This scheme is shown in the following table. It will be noted that Bandelier and Roepke's scheme approximates to No. 6 of Pope's scale, which gives six doses in each dilution. It is impossible to measure accurately the

14 PRELIMINARY REPORT ON TUBERCULIN

small increases of doses given in Pope's scales in syringes graduated in 10ths or 20ths, graduations of 100ths being necessary.

I have dealt somewhat fully with this question of dosage, as I have to refer to it again later in this report when discussing the progress made by various types of case.

POPE'S SCALE OF DOSES

2	3	4	5	6	7	8	9	10	11	12
1	1	1	1	1	1	1	1	1	1	1
3.2	2.2	1.8	1.6	1.5	1.4	1.3	1.3	1.3	1.2	1.2
10	4.7	3.2	2.5	2.2	2.0	1.8	1.7	1.6	1.5	1.5
	10	5.6	4.0	3.2	2.7	2.4	2.2	2.0	1.8	1.8
		10	6.3	4.7	3.7	3.2	2.8	2.5	2.3	2.2
			10	6.8	5.2	4.2	3.6	3.2	2.9	2.6
				10	7.2	5.6	4.7	4.0	3.5	3.2
					10	7.5	6.0	5.0	4.3	3.8
						10	7.7	6.3	5.3	4.7
							10	8.0	6.6	5.6
								10	8.0	6.8
									10	8.3
										10

(5) *Intervals between Doses*

The usual practice in this respect has been followed so far as it can be said that there is really a general rule. The dosage is a matter for decision in each case. For the most part, with the afebrile cases, an interval of two days was allowed, thus ensuring three inoculations a week. This interval, or one of three days, can often be maintained up to the 1 in 100 dilution, or further. As the stronger dilutions are reached, the intervals are gradually lengthened to four days and upwards, and when using undiluted tuberculin an interval of seven days or more is generally allowed.

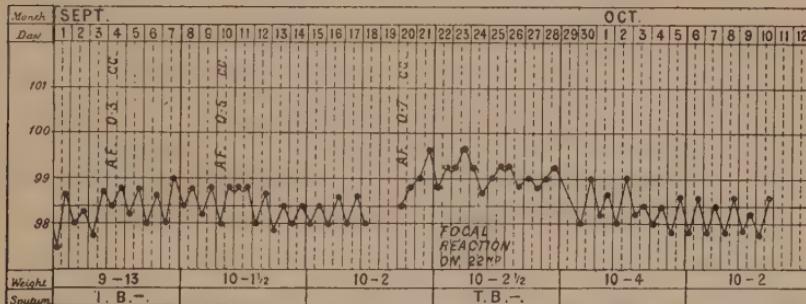
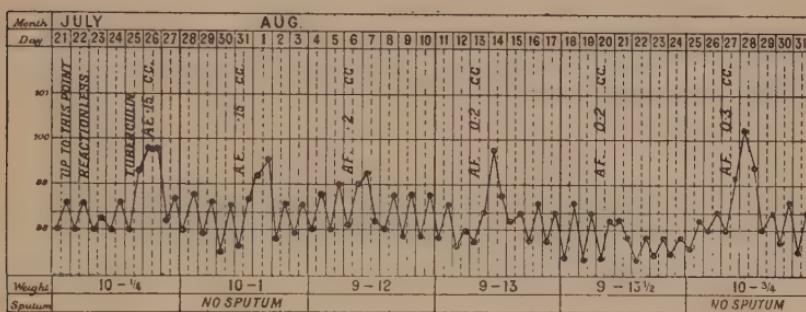
(6) *The Maximum Dose*

One c.c. of tuberculin is regarded as the maximum dose, i.e. however great the tolerance to tuberculin manifested, a higher dose than 1 c.c. is believed to be of no

PRELIMINARY REPORT ON TUBERCULIN 15

advantage. This does not mean that 1 c.c. of tuberculin is the dose to be aimed at, even at the risk of inducing reactions; a tolerance to such a high dose is not certainly of greater value than tolerance to a somewhat smaller dose, such as '1 c.c. or '01 c.c. Many patients can receive the latter without the production of reactions, whereas

CHART 2.



intolerance and repeated reactions would follow higher doses. The physician may experience a sense of satisfaction when the full 1 c.c. can be borne, but this should not tempt him to persevere with increasing doses in the face of increasing intolerance; under such circumstances, it is far better to discontinue the course, and to begin another with a lower initial dose.

Some of our earlier records, of which the following (see

16 PRELIMINARY REPORT ON TUBERCULIN

Chart 2) is an example, reflect this desire to reach the maximum dose of 1 c.c. In this case, the course had been reactionless up to '1 c.c., and the treatment had been successful, as by the time this dose was reached tubercle bacilli had disappeared from the sputum. To a dose of '15 c.c., the patient reacted ; to '2 c.c. there was again some reaction, and this dose had to be repeated twice before it was well tolerated. To '3 c.c. there was again a reaction, but a similar dose a week later was well tolerated. The dose of '5 c.c. was also well tolerated, but to '7 c.c. ten days later there was a prolonged reaction, associated with a definite focal reaction in the diseased lung. In this particular case, no harm resulted, but it would have been better to have discontinued the course at the first reaction, and after a short interval to have begun another course at a lower level of dosage.

(7) *Limit of Tolerance*

A point is arrived at in the treatment of nearly all cases, however well they tolerate tuberculin, beyond which it is difficult to give increasing doses without fear of a reaction. The proper maximum dose, therefore, for every case is the highest which is well tolerated.

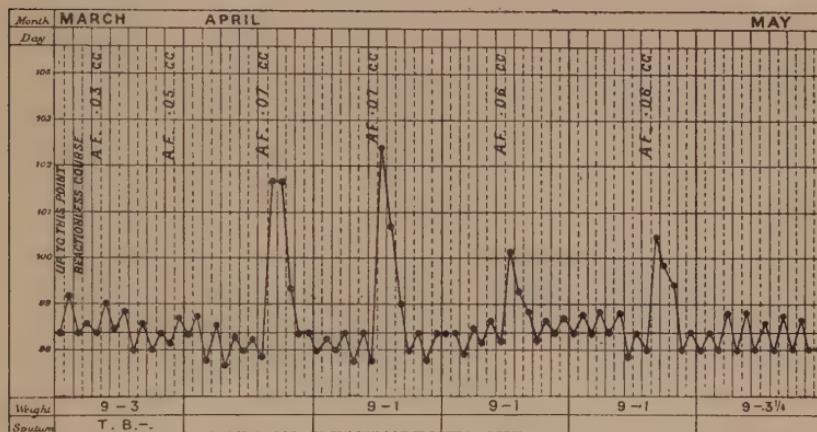
Not infrequently signs of intolerance are first met with when the dilution of 1 in 10 is reached. This differs from the intolerance (hypersensitiveness) not uncommonly met with during the initial stages of a course, which can nearly always be overcome.

Chart No. 3 illustrates the sudden development of intolerance. In this case, the disease was of recent origin and limited in area. The course had been reactionless and in every way satisfactory up to a dose of '05 c.c. A.F., and T.B. had disappeared from the sputum. To '07 c.c. there was a considerable reaction, and a repetition of this dose, after an interval of five days, again produced a reaction. A reduction to '06 c.c. was again followed by

PRELIMINARY REPORT ON TUBERCULIN 17

a reaction, although it was less marked : the treatment was then discontinued. Nothing worse resulted than malaise and loss of weight of quite a temporary character, and a week after leaving off tuberculin, the general health was re-established and the patient was discharged apparently well. There is no doubt that to terminate the

CHART 3.



inoculations was the correct course to take, though if the patient had been able to stay longer in the sanatorium, she would have been given a course of B.E., beginning with a low dose.

Increasing experience has convinced us that when the stronger doses are reached, namely, 1 in 10 or even 1 in 100, any tendency to reaction is evidence that the maximum dose, or, as it is better termed, the optimum dose (for the particular patient) has been reached.

(8) *Sensitiveness during Treatment*

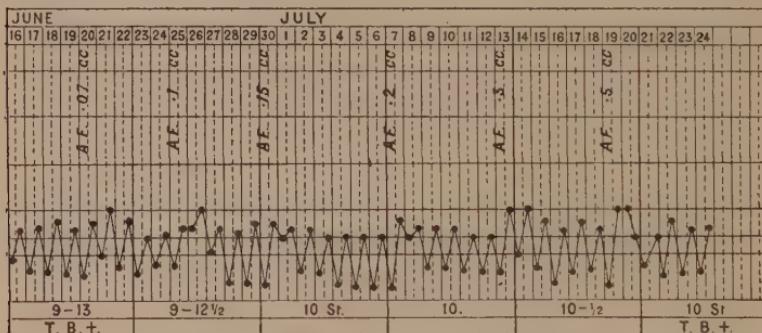
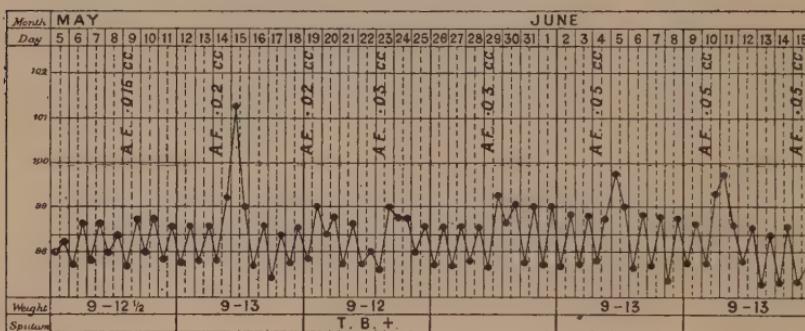
Very similar to the condition just described is a temporary period of intolerance, which sometimes develops when moderately high doses are reached. This can often

18 PRELIMINARY REPORT ON TUBERCULIN

be got over by careful management in the matter of repeating the doses, lengthening the intervals or going back to a smaller dose. Once safely through this period, it is usually possible to proceed to considerably higher doses without any ill effect.

The record on the following chart (No. 4) is a good illustration of this point:

CASE 1. CHART 4.



CASE 1

This patient had a very slight lesion at one apex, and was in excellent general health, a type of case which usually can be given a full course of tuberculin without trouble. The course was reactionless up to a dose of

·015 c.c. The next inoculation, ·02 c.c., was followed by a sharp reaction, the temperature rising to 101·2°. This period of intolerance lasted for four weeks, necessitating great care, but from that point the patient was quite tolerant and went steadily through the full course up to 1 c.c. without any tendency to reaction. The development of sensitiveness of this character is an interesting but troublesome feature in the treatment, and calls for the exercise of judgment. It is necessary to decide whether the reactions are due to a sensitiveness which can in all probability be removed by care, or whether they indicate that the limits of tolerance have been reached. The general clinical condition of the patient is probably the safest guide under such circumstances. In the case just described, the first inoculation which caused a well-defined reaction, namely ·02 c.c., was not the optimum dose, but had the patient's condition been less favourable, increasing doses would not have been given.

To obtain an impression of the average maximum dose for favourable cases, I would refer the reader to the table on page 21 of this report, which gives the maximum and minimum doses which were administered to the 42 patients who lost their bacilli. The final doses in these tables do not necessarily mean that they were the maximum doses considered to be desirable, as many of these patients left the sanatorium before this point was reached. When, however, a course of two varieties of tuberculin was given, the final dose of the first course represents the maximum dose considered to be suitable.

Bearing this point in mind, it will be observed that the final doses were as follows :

1 c.c., 1 c.c., ·3 c.c., ·005 c.c., 1 c.c., ·0003 c.c., ·5 c.c., ·05 c.c., ·8 c.c., ·75 c.c., ·01 c.c., ·2 c.c., ·1 c.c., ·025 c.c., ·06 c.c., ·015 c.c., and ·01 c.c.

The "optimum" dose for the less favourable cases is considerably lower.

SECTION V

Courses of Tuberculin Injection

On 42 Cases in which injections of Tuberculin were not followed by Reactions

IT would seem remarkable that upon such an essential point as the safety or danger of producing a reaction, there should be such divergence of opinion. When two opposite opinions are held on a subject, it may indicate that evidence is forthcoming to support both views. I propose briefly to consider the evidence afforded by the records of 42 patients who lost their bacilli, and who, whilst undergoing tuberculin treatment, followed the ordinary routine of sanatorium treatment, and were fully restored to general health and capacity for work.

Attention is naturally turned to the records of these cases in order to note what factors, if any, they had in common, and amongst others, to what extent their tuberculin courses were reactionless or otherwise. These patients, 42 in number, had altogether 1,229 inoculations, of which only 48, or 3·9%, gave rise to a general reaction as evidenced by a rise of temperature of 1° F. Further, of these 48 general reactions, 14 only were accompanied by an obvious focal reaction in the diseased area. On the accompanying table, the details are given of the analysis upon which these figures are based :

PRELIMINARY REPORT ON TUBERCULIN 21

PATIENTS WHO LOST THEIR T.B. DURING TREATMENT

No. of Case	Record of Tuberculin Dosage and Number of Reactions.					
	Tub.	Min. Dose.	Max. Dose.	General Reactions.	Focal Reactions.	Notes.
1	A.F.	c.c.	c.c.			
2	A.F.	.0001	.2	5	—	Reactionless to .05.
3	A.F.	.00001	.0002	—	—	
3	A.F.	.0001	1	—	—	T.B. lost on A.F.
3	B.E.	.002	.01	—	—	
4	T.R.	.0002	1	4	—	T.B. lost on T.R.
4	A.F.	.001	1	—	—	
5	A.F.	.00001	.02	—	—	
6	A.F.	.00002	.3	—	—	T.B. lost on A.F.
6	B.E.	.00002	.01	1	—	
7	B.E.	.00005	.005	3	—	T.B. lost on A.F.
7	A.F.	.005	.007	—	—	
8	A.F.	.0001	.15	—	—	
9	A.F.	.00001	.006	—	—	
10	T.R.	.0002	.002	—	—	
11	A.F.	.0001	1	—	—	
12	A.F.	.0001	1	6	—	Reactionless to 1 c.c.
12	B.E.	.001	.007	—	—	T.B. lost on A.F.
13	A.F.	.0001	.04	—	—	
14	B.E.	.00005	.0015	3	2	T.B. lost on A.F.
15	A.F.	.0001	.0003	1	1	T.B. lost on A.F.
15	B.E.	.0005	.003	—	—	
16	A.F.	.00001	.5	—	—	T.B. lost on A.F.
16	B.E.	.0002	.08	—	—	
17	A.F.	.0002	.05	—	—	
18	A.F.	.00001	.8	—	—	T.B. lost on A.F.
18	B.E.	.0001	.0015	—	—	
19	A.F.	.00001	.75	—	—	T.B. lost on A.F.
19	B.E.	.001	.05	—	—	
20	B.E.	.00001	.007	4	2	Reactionless to .003: T.B. lost before first reaction.
21	A.F.	.00001	.01	—	—	T.B. lost on A.F.
21	B.E.	.002	.01	5	5	Reactions all on B.E. after loss of T.B.
22	A.F.	.0001	.2	2	—	Reactionless to .2
22	B.E.	.0005	.1	—	—	A.F.: T.B. lost before first reaction
23	A.F.	.000005	1	2	—	
24	A.F.	.00005	.06	—	—	
25	A.F.	.0001	.005	1	—	
26	A.F.	.00001	.03	—	—	
27	A.F.	.00001	.75	—	—	
28	A.F.	.000005	.005	—	—	
29	A.F.	.00005	.1	—	—	T.B. lost on B.E.
29	B.E.	.002	.02	—	—	

22 PRELIMINARY REPORT ON TUBERCULIN

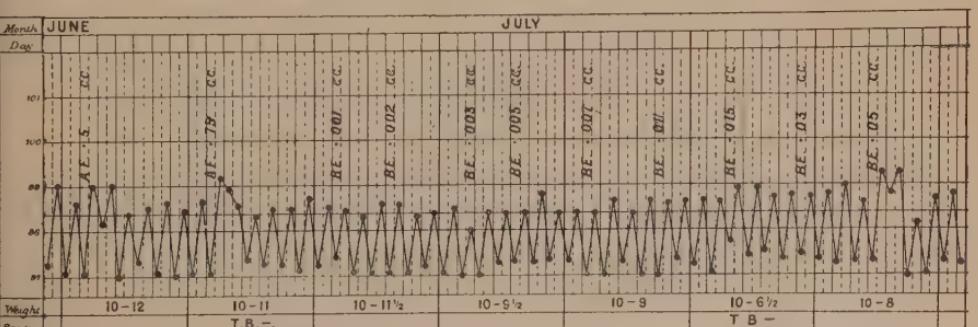
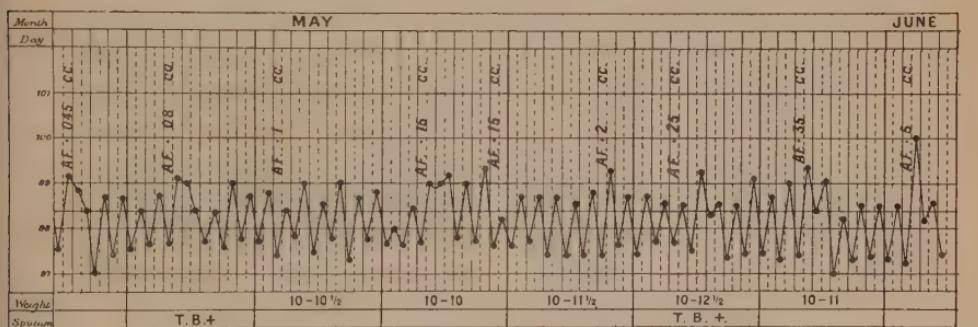
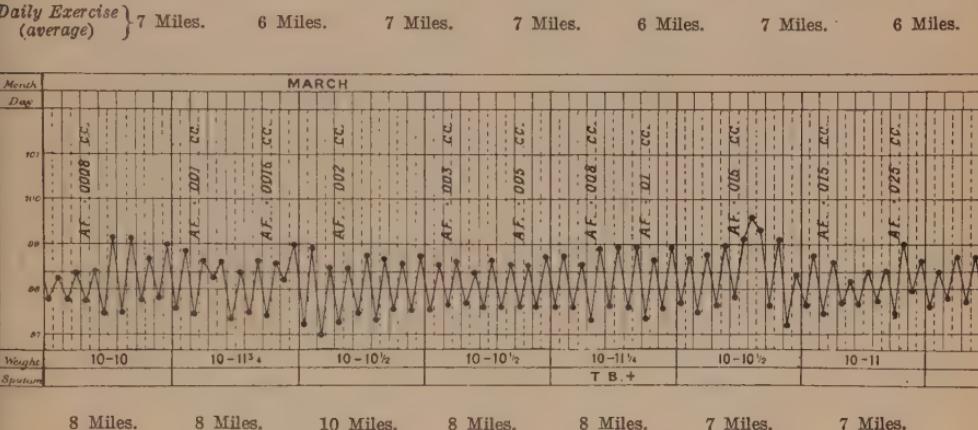
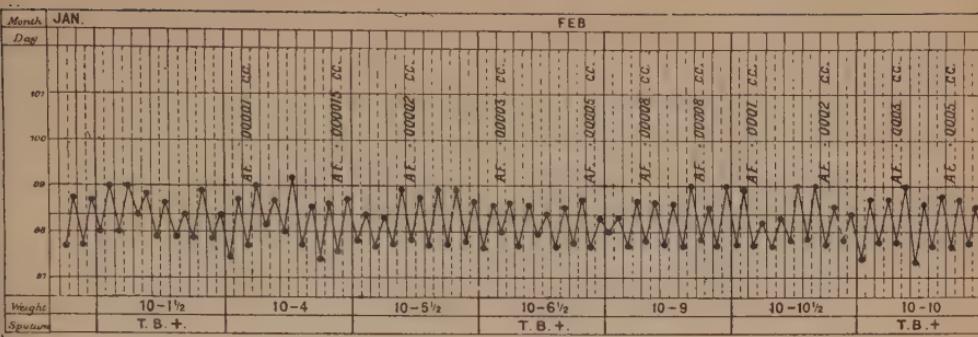
No. of Case.	Record of Tuberculin Dosage and Number of Reactions.					
	Tub.	Min. Dose.	Max. Dose.	General Reactions.	Focal Reactions.	Notes.
30	A.F.	·0001	·1	—	—	
31{	B.E.	·00001	·025	—	4 (slight)	T.B. lost on A.F.
	A.F.	·002	·006	—	—	
32	B.E.	·00001	·0001	—	—	
33	A.F.	·0001	·3	3	—	
34	B.E.	·00001	·00008	—	—	
35	A.F.	·00005	·001	—	—	
36{	A.F.	·00001	·001	—	—	Reactionless to ·06 A.F.
	A.F.	·0001	·06	2	—	
37{	B.E.	·00005	·004	—	—	T.B. lost before first reaction.
	A.F.	·00001	·015	1	1	
38{	B.E.	·0005	·0015	—	—	T.B. lost on B.E.
	A.F.	·0001	·7	4	2	
39	A.F.	·00001	·01	—	—	Reactionless to ·15. T.B. lost on A.F.
40{	B.E.	·0005	·003	1	1	
	A.F.	·0001	·0007	—	—	
41{	A.F.	·000005	·7	4	4	}T.B. lost on A.F.
	B.E.	·001	·02	—	—	

The treatment of these 42 patients, taken collectively, was in all probability as free from reactions as is possible with the method of administration adopted. Such reactions as occurred, moreover, were in nearly every case produced by the higher doses, when the optimum dose for the particular patient was being approached, and after T.B. had ceased to be found in the sputum. A favourable result had already been accomplished, namely, loss of T.B., disappearance of symptoms of disease, and the restoration of general health.

It is significant that, without any exception, the cases which were thus successfully treated on ordinary sanatorium lines, plus tuberculin, should have had reactionless courses, and that no case which was troublesome to immunise on account of reactions was successful as judged by the loss of bacilli.

One factor, then, which all these cases had in common

CASE 2. CHART 5.



* 7 Miles. 8 Miles. 8 Miles. 10 Miles. 10 Miles. 8 Miles. 8 Miles.

* Away 2 days

24 PRELIMINARY REPORT ON TUBERCULIN

was a capacity to take increasing doses of tuberculin without reactions. The treatment of these cases presented no difficulty whatever. With scarcely a flicker of the temperature curve, without any symptoms, such as malaise, etc., these patients were able to pursue exactly the same course of general treatment as had always been prescribed to favourable cases at the sanatorium before the days of tuberculin. In particular, in respect to exercise, these patients were able to follow out the full course of steadily increased exercise, and many of them, throughout their specific treatment, were working in the gardens every morning, and walking from 4 to 6 miles every afternoon. One modification only was made in the usual routine, it being our practice, as a precautionary measure, to reduce the exercise somewhat on the day of inoculation.

Amongst these 42 cases there were wide variations as to the amount of lung involved by the disease. In some of them the lesions were only slight, in others of moderate extent, in one at least the disease was extensive. As already stated, they all had T.B. in their sputum when first admitted, but they all had as a common factor that quality of constitutional stability which betokens the existence of natural resistance and power of recuperation, and in virtue of this characteristic they were all what would be termed favourable cases.

The following are typical examples of the progress made by such cases. The records of the remaining 38 cases of this class are similar in all essentials :

CASE 2

With accompanying chart (No. 5), showing records of temperature, weight, sputum, exercise, and dosage.

Male aged 21 years.—Admitted January 3rd, 1912.

Pulmonary Disease.—Infiltration of the upper third of the upper and lower lobes of the right lung.

PRELIMINARY REPORT ON TUBERCULIN 25

General Condition.—Favourable ; afebrile ; 10 lb. above average normal weight.

Sputum.—Small in amount, containing T.B.

Tuberculin Treatment.—The first course was commenced on January 16th with '00001 c.c. A.F., and ended June 17th with '75 c.c. A second course was commenced on June 24th with '001 c.c. B.E., and ended on July 24th with '05 c.c. In all the 2 courses lasted 28 weeks, during which 42 inoculations were given. Both were reactionless, and in the absence of febrile disturbances the patient throughout the whole of his stay in the sanatorium was able to take a full measure of exercise, namely 10 to 12 miles' walking daily, or, as an alternative, working in the grounds in the morning and walking 5 to 6 miles in the afternoon. He was discharged on July 20th apparently well, and returned to his ordinary work. T.B. were not found in the sputum after May 21st.

The details of the tuberculin injections are added, as they give a good view of a suitable method of dosage for the type of patient who can undergo tuberculin treatment without risk and possibly with advantage.

Jan. 15.	'00001 c.c., A.F.	Mar. 21.	'005 c.c., A.F.
20.	'000015	26.	'008
24.	'00002	29.	'01
29.	'00003		
Feb. 3.	'00005 c.c., A.F.	April 3.	'015 c.c., A.F.
6.	'00008	8.	'015
9.	'00008	12.	'025
12.	'0001	17.	'045
16.	'0002	23.	'08
20.	'0003	29.	'1
23.	'0005		
27.	'0008	May 7.	'15 c.c., A.F.
Mar. 4.	'001 c.c., A.F.	11.	'15
8.	'0015	17.	'2
12.	'002	21.	'25
18.	'003	28.	'35

26 PRELIMINARY REPORT ON TUBERCULIN

June	3.	·5 c.c., A.F.	July	4.	·005 c.c., B.E.
	10.	·5		8.	·007
	17.	·75		12.	·01
		End of A.F. course.		16.	·015
	24.	·001 c.c., B.E.		20.	·03
	27.	·002		24.	·05
	31.	·003			Patient discharged.

CASE 3

Male aged 25 years.—Admitted August 28th, 1911.

Pulmonary Disease.—*Right lung*, signs of recent disease in upper lobe to third rib; also in middle lobe and in upper third of lower lobe. *Left lung*, loss of resonance at the apex, due probably to an old lesion.

General Condition.—Favourable; weight up to normal; T.B. present.

This patient, treated on ordinary sanatorium lines up to the end of December (4 months) was by then convalescent, working in the garden every morning, and walking six miles in the afternoon.

The physical signs in the lungs were much less marked, but the sputum still contained T.B.

Tuberculin Treatment.—The first course was commenced on January 2nd with ·000005 c.c. A.F., and finished on May 30th with 1 c.c.

A second course was commenced on June 10th with ·002 c.c. B.E., and finished on June 25th with ·02 c.c.

In all the tuberculin treatment lasted 23 weeks, during which 37 inoculations were given. Both courses were without reaction, and, as in the last case, the patient throughout continued the same exercise he had previously taken, namely, work in the gardens and walking. At no time was there any malaise or other evidence of toxic effects.

PRELIMINARY REPORT ON TUBERCULIN 27

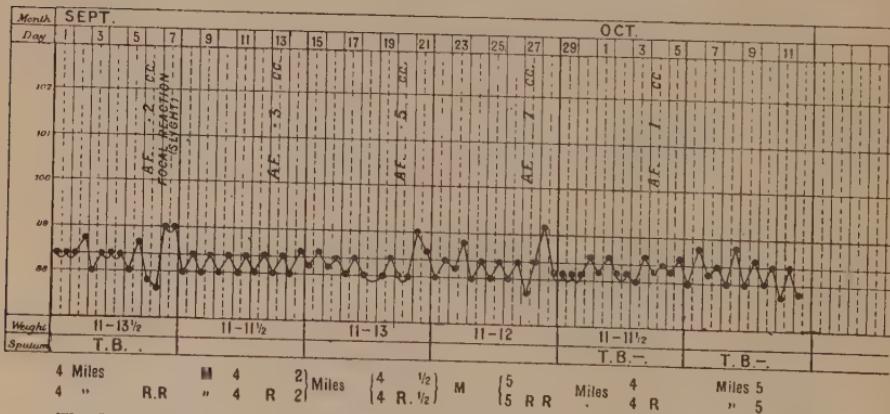
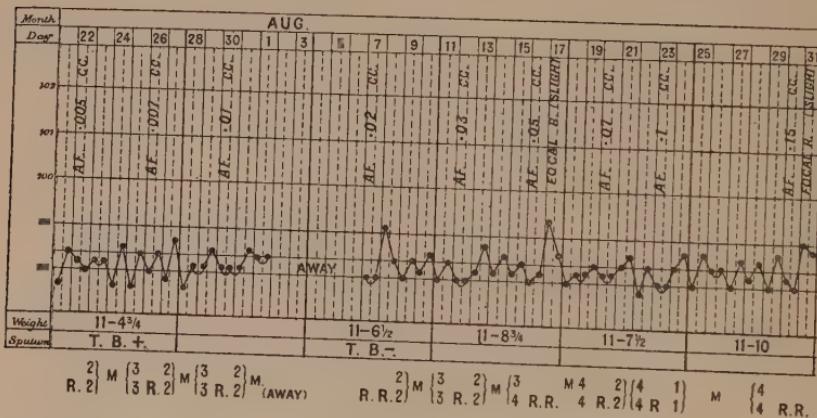
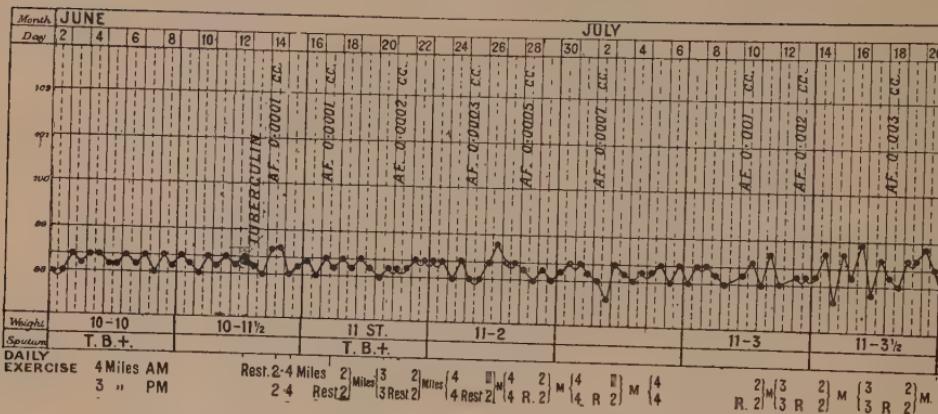
The actual doses were as follows :

Jan.	1.	·000005 c.c., A.F.	Mar.	20.	·01 c.c., A.F.
	6.	·00001		26.	·015
	10.	·000015		30.	·02
	15.	·00002			
	20.	·00003	April	3.	·03 c.c., A.F.
	24.	·00005		10.	·05
	29.	·00008		15.	·08
				20.	·15
Feb.	2.	·0001 c.c., A.F.		27.	·25
	6.	·0001			
	9.	·00015	May	7.	·4 c.c., A.F.
	12.	·0002		13.	·4
	15.	·0003		20.	·7
	20.	·0005		30.	1 c.c.
	23.	·0008			End of A. F. course.
	26.	·001			
Mar.	1.	·0015 c.c., A.F.	June	10.	·002 c.c., B.E.
	4.	·002		14.	·005
	8.	·003		18.	·008
	12.	·005		21.	·01
	16.	·008		25.	·02

T.B. were last found on May 21st, and frequent examinations from that date until the patient's discharge, on June 30th, were negative. On his discharge, the patient was in the same condition as before the tuberculin treatment was commenced, but the T.B. had disappeared from the sputum.

The next chart (No. 6) is typical of a practically reactionless course up to 1 c.c. of undiluted tuberculin. The patient was a man of good physique and of vigorous constitution, and the disease was in an early stage.

CHART 6.



The dose on Sept. 27 was 7 c.c., not 7 c.c., and the sputum under Sept. 3 should be T.B.

SECTION VI

(a) Cases in which there was a Slight Response to Tuberculin short of an Objective Reaction

Most of the cases thus treated gave evidence from time to time of response to tuberculin. Such evidence consisted of a slight rise of the temperature on waking, on the morning following the inoculation. For example, instead of the usual rectal temperature at 7.30 a.m. of about 97.6° F. (the average rectal temperature of a normal person on waking) a temperature of 98.6° would be recorded, though by midday the temperature would have regained the normal level. Temperatures taken in the mouth are nearly a degree lower, but the ratio remains the same. This slight rise of temperature on waking is the only obvious indication of response to an inoculation, there being no associated symptoms, and if there is such a thing as a laudable reaction, this represents it, and we have come to recognise it as being no contra-indication of satisfactory progress. If the response is more pronounced, the temperature thus slightly raised in the morning remains above its usual normal level at midday, sometimes also until the evening, touching perhaps 99.6° F. before it drops, but again the rise is unassociated with any symptoms, and but for the temperature record the patient would not be aware of any effects of the inoculation.

Chart 7, facing page 30, illustrates these points.

It will be noticed that there was a slight rise of the "waking temperature" on December 14th, 18th, 21st,

30 PRELIMINARY REPORT ON TUBERCULIN

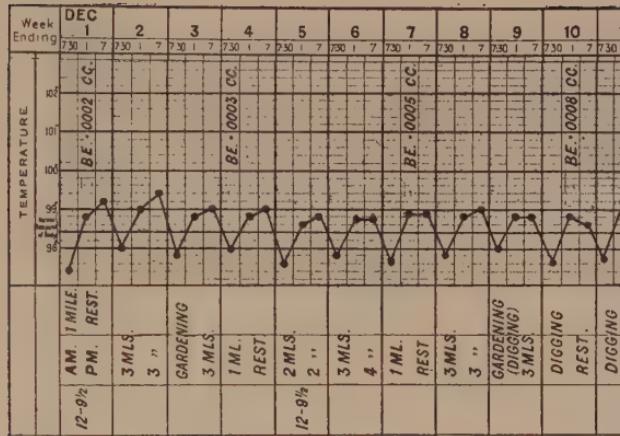
29th, January 2nd, etc., in each case on the day following an inoculation ; later on, the rise was somewhat more pronounced and sufficiently marked to represent an objective reaction. Full exercise was taken throughout, and the reaction disappeared within 24 hours.

The upper half of Chart 7 shows more clearly than any written description the type of response to tuberculin which is safe, whilst the lower half of the chart shows the type of response which in favourable cases is permissible, but beyond which it is not safe to go.

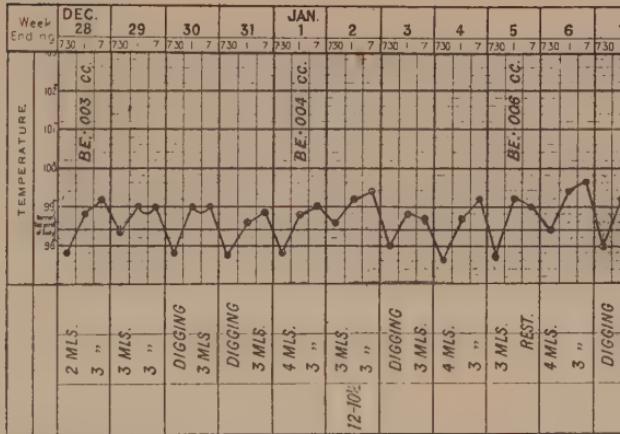
(b) Cases which show that the Absence of Reactions during a Course of Injections lasting for many months is not necessarily followed by demonstrable Benefit

Before leaving this subject of reactionless treatment it should be made quite clear that although complete recovery is compatible with a reactionless course of tuberculin when given at the same time as ordinary sanatorium treatment, it is by no means certain that a prolonged reactionless course of treatment will result in any positive gain. On the contrary, many cases take tuberculin just as well as the 42 cases under consideration, but without apparent benefit ; that is to say, their progress is identical with the progress made by those treated without tuberculin which do not lose T.B. There is one difference only, in that they are rendered tolerant to considerable doses of tuberculin. This may possibly be an advantage, provided that the tolerance thus acquired is maintained by post-sanatorium inoculation. Without this after-treatment the advantages are probably negligible.

The following cases are typical of those in which T.B. persisted in the sputum after tolerance to large doses of tuberculin had been established.



Shows the type of reaction which is permissible, and which occurs in *ne* rise of the temperature on waking on the morning following the inoculation in any way. In the particular case illustrated the patient was digging in t



Illustrates the limits of a reaction which is permissible in the most favourable case, i.e., when the temperature remains raised the whole day. There is, however, a complete absence of

CASE 4

Moderately advanced disease of 4 years' duration, with a considerable degree of arrest.

General condition favourable. Weight above normal.
No pyrexia.

Length of tuberculin treatment, 47 weeks.

No. of inoculations, 62.

Course almost reactionless.

Discharged much improved, T.B. still present.

CASE 5

Moderately advanced disease of 18 months' duration.

General condition favourable. Weight well above normal.

No pyrexia.

Length of tuberculin treatment, 57 weeks.

No. of inoculations, 57.

Course almost without reaction.

Discharged much improved, T.B. still present.

CASE 6

Moderately advanced disease of 3 years' duration, with considerable degree of arrest.

General condition favourable. Weight normal. No pyrexia.

Length of tuberculin treatment, 45 weeks.

No. of inoculations, 51.

Course practically reactionless.

Discharged much improved, T.B. still present.

CASE 7

Moderately advanced disease of 6 months' duration.

General condition favourable. Weight a little below normal. No pyrexia.

Length of tuberculin treatment, 31 weeks.

32 PRELIMINARY REPORT ON TUBERCULIN

No. of inoculations, 41.

Reactionless course.

Discharged much improved, T.B. still present.

CASE 8

Moderately advanced disease of 18 months' duration, with tuberculosis of larynx.

General condition favourable. Weight normal. No pyrexia.

Length of tuberculin treatment, 36 weeks.

No. of inoculations, 37.

Course practically reactionless.

Discharged much improved, T.B. still present.

CASE 9

Moderately advanced disease of 6 months' duration.

General condition favourable. Up to weight. Afebrile.

Length of tuberculin treatment, 30 weeks.

No. of inoculations, 31.

Course practically reactionless.

Discharged much improved, T.B. still present.

CASE 10

Moderately advanced disease of 6 months' duration.

General condition favourable. Weight normal. Afebrile.

Length of tuberculin treatment, 32 weeks.

No. of inoculations, 40.

Course almost reactionless.

Discharged much improved, T.B. still present.

CASE 11

Moderately advanced disease of 12 months' duration.

General condition favourable. Weight normal. Afebrile.

Length of tuberculin treatment, 29 weeks.

PRELIMINARY REPORT ON TUBERCULIN 33

No. of inoculations, 32.

Course almost reactionless.

Discharged much improved, T.B. still present.

CASE 12

Moderately advanced disease of 2 months' duration.

General condition favourable. Above normal weight.

Afebrile.

Length of tuberculin treatment, 35 weeks.

No. of inoculations, 36.

Reactionless course.

Discharged much improved, T.B. still present.

Many other cases in this series are very similar to the above.

SECTION VII

Cases in which Marked Reactions followed Injections of Tuberculin

I HAVE been able to extract from our records sufficient evidence to prove conclusively that reactions are a source of danger. Fortunately the evidence is not extensive, for our practice has been to discontinue tuberculin as soon as it is evident that it cannot be given without risk.

The following is the record of a case in which a focal reaction followed an inoculation, and produced a definite relapse.

CASE 13 (CHART 8)

Miss X. Admitted July 1912.

Type of Case.—Advanced disease of 18 months' duration, with a considerable degree of arrest.

General Condition.—Favourable. Weight 7 lb. above her average normal. Temperature 98.4° a.m. to 99.6° p.m.

Sputum.—About 3 oz. daily, containing T.B.

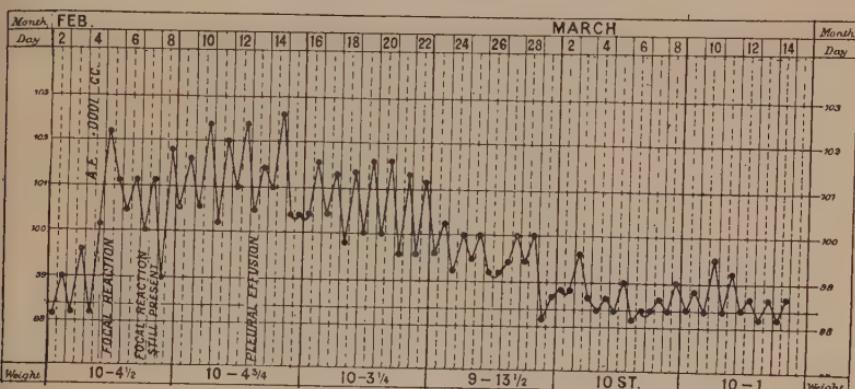
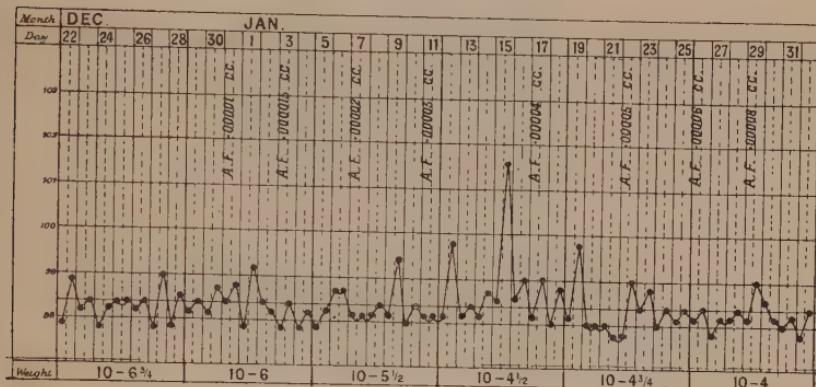
For 15 weeks this patient was treated on general sanatorium lines, and improved in all respects. The progress is well shown by the fact that, commencing with exercise of 1 mile daily, by the end of 15 weeks she was walking 8 or 9 miles with satisfactory results and with a normal temperature. At this date there were fewer adventitious sounds, and there were signs which probably indicated increased fibrosis. The sputum was reduced by one-half.

PRELIMINARY REPORT ON TUBERCULIN 35

Tuberculin treatment was then begun in the hope of clearing the sputum of T.B., the initial dose being .00001 c.c. A.F.

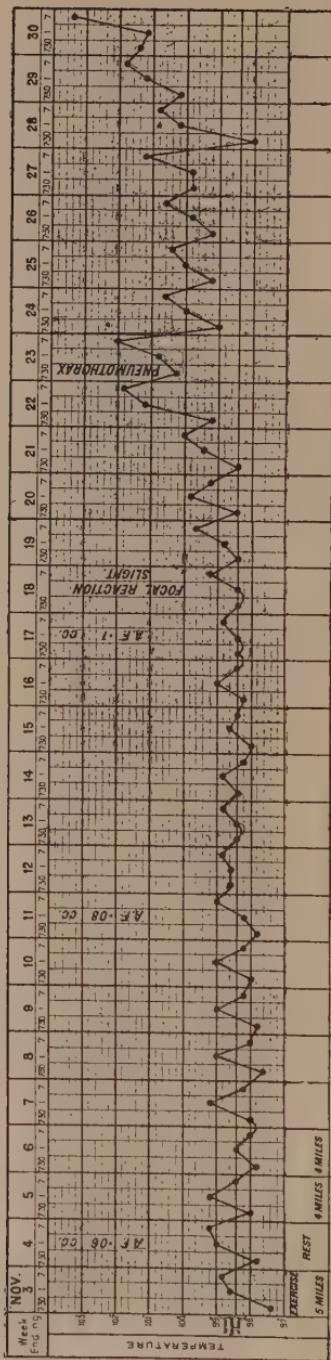
The first three doses were well tolerated. The fourth dose, of .00003 c.c., produced a slight rise of temperature,

CASE 13. CHART 8.

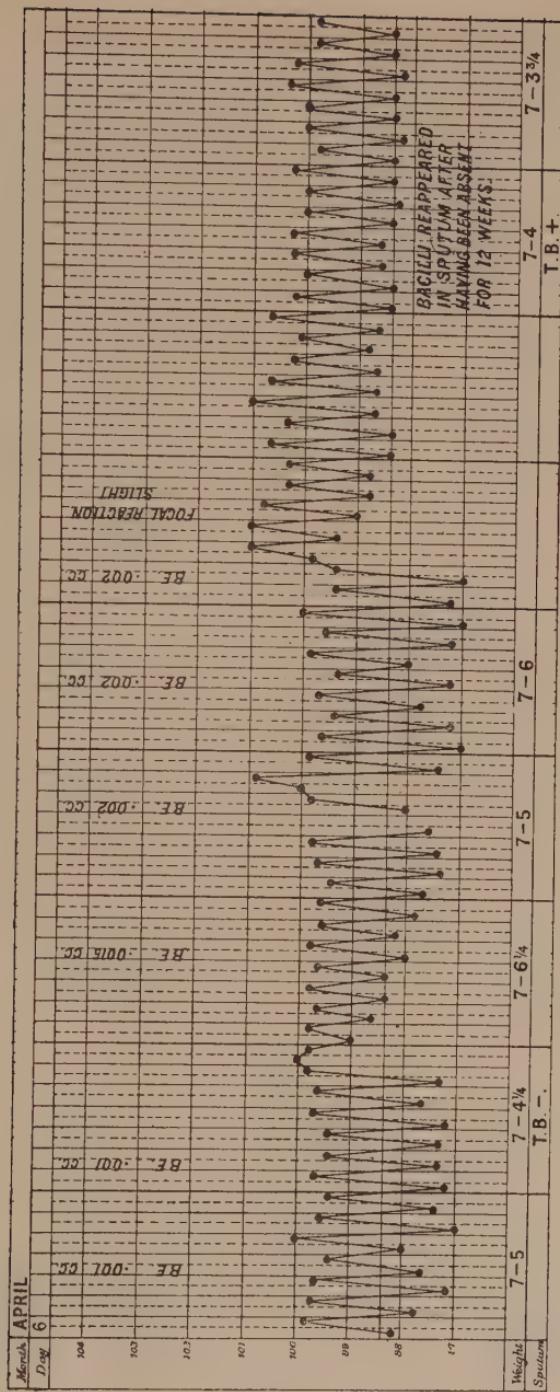


and three days later there was a sharp rise of temperature, with a fall to normal on the following day ; this seemed to be independent of the injections. The next dose, of .00004 c.c., produced some increase of cough and sputum, and a temperature reaction to 99.8° F. The next three

CASE 14. CHART 9.



CASE 15. CHART 10.



38 PRELIMINARY REPORT ON TUBERCULIN

doses produced no traces of reaction, but the dose following, namely, '0001 c.c., given after an interval of 5 days, produced a sharp rise of temperature associated with a focal reaction. The temperature remained up, and in the course of a few days a pleural effusion developed at the left base. This febrile relapse lasted for about 5 weeks, when convalescence was slowly re-established; on the patient's discharge some two months later the lung-condition was similar to what it had been before tuberculin treatment was begun. But the general condition of the patient was not quite so satisfactory.

CASE 14

Chart No. 9 is that of a case in which a pneumothorax followed closely, and was associated with, a slight focal reaction. A disquieting feature of this case was that the reaction which preceded the pneumothorax was similar to other trifling reactions which had occurred in an otherwise reactionless course of 31 weeks' duration. Previous to this reaction there had only been evidence of chronic disease of moderate extent, and, as the chart shows, there was no fever, and the patient was able to walk 4 or 5 miles daily. The association of the reaction and the pneumothorax may of course have been a mere coincidence.

CASE 15

Chart No. 10 is an illustration of a reaction ushering in a period of increased fever associated with signs of greater activity of the disease. The case was an unfavourable one, 10 weeks of general treatment having failed either to bring about any improvement or to reduce the temperature below a range of 97° a.m. to 100° p.m.

Tuberculin (B.E.) was then given in the hope of lowering

the temperature, and for a time it appeared to do so. The chart begins at the tenth week of tuberculin treatment, up to which point there had been nothing to indicate a reaction. Slight signs of intolerance to a dose of '002 c.c., given in the fourteenth week, did not recur, when the same dose was repeated a few days later. A similar dose, however, was repeated, and this time it was followed by a febrile disturbance, which lasted for 5 weeks. During this period adventitious sounds were heard over an extended area of the chest, and T.B., which had been absent from the sputum for 12 weeks, reappeared.

CASE 16

Chart No. 11 shows that a pleural effusion may follow a focal reaction, a result frequently observed when tuberculin was first introduced. On admission, there were signs of moderately extensive disease in the upper and lower lobes of the right lung, with signs suggestive of early disease of the apices of both lobes of the left lung. The general condition was fairly good, the temperature was rather unsteady, and the weight was 8 lb. below the normal average.

After 5 weeks of general treatment, '00001 c.c. A.F. was given, and the course was reactionless up to '01 c.c., given 14 weeks later. In the meantime, progress was very satisfactory. There was gain of weight of 9 lb.; the temperature remained steady with a normal range, and exercise was gradually increased up to 6 miles daily. After the dose of '01 c.c., there was a lessened degree of tolerance. For example, after '015 c.c., there was a reaction to 100° F.; on repetition of the dose, there was a slight reaction to 99.4° F., but a second repetition of the dose was well tolerated. With '02 c.c., there was a reaction to 100.4° F., the temperature falling to

40 PRELIMINARY REPORT ON TUBERCULIN

normal on the following morning. Neither malaise nor increase of sputum was associated with any of these reactions. A repetition of '02 c.c. was well tolerated, but '03 c.c. again produced a slight reaction. A repetition of this dose a week later produced no reaction at all, except that there was a rise of temperature on waking. Three days later the temperature rose rapidly, and this was the beginning of a febrile relapse lasting 6 weeks. During this relapse a slight pleural effusion developed at the left base.

This case shows very well the risk that is incurred when the strictly reactionless course is departed from.

CASE 17

Chart No. 12 records the most serious effect which has been observed in any of our cases treated with tuberculin, and the experience has left a deep impression of the risks attaching to the use of tuberculin.

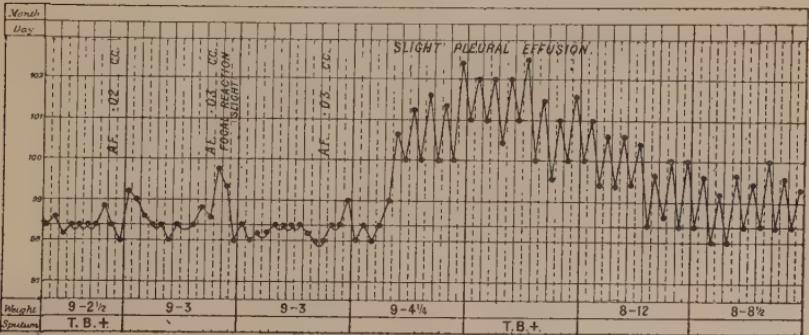
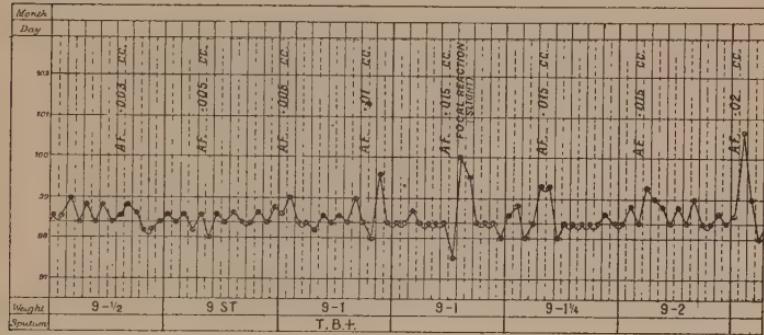
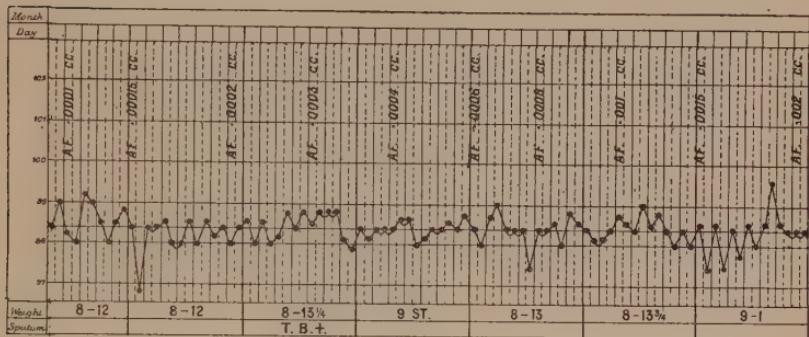
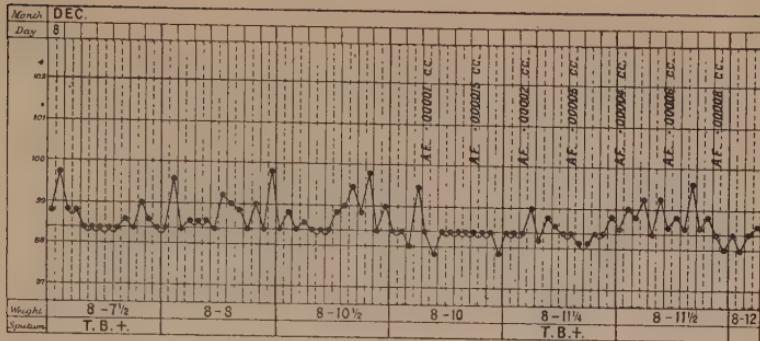
The patient, Mr. A, aged 30, was admitted in December 1912. There was a history of haemoptysis 6 months before admission.

The case was one of moderately advanced disease. No evidence of disease was detected in the right lung. In the left, there was loss of resonance from the apex of the upper lobe to the third rib, with a few crepitations at the apex, and in the lower lobe, impairment of resonance at the apex, with a few crepitant râles on cough.

The patient's general condition was good. Weight, 3 lb. above his average. Temperature normal. There were only traces of sputum, which contained tubercle bacilli.

Treatment.—For 6 weeks he was treated on ordinary sanatorium lines. He was at this time quite convalescent, walking 8 miles a day, and the case was in every way

CASE 16. CHART 11.

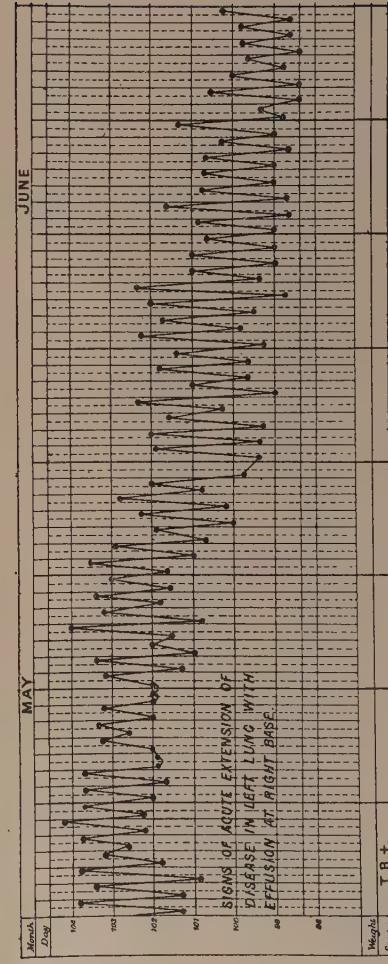
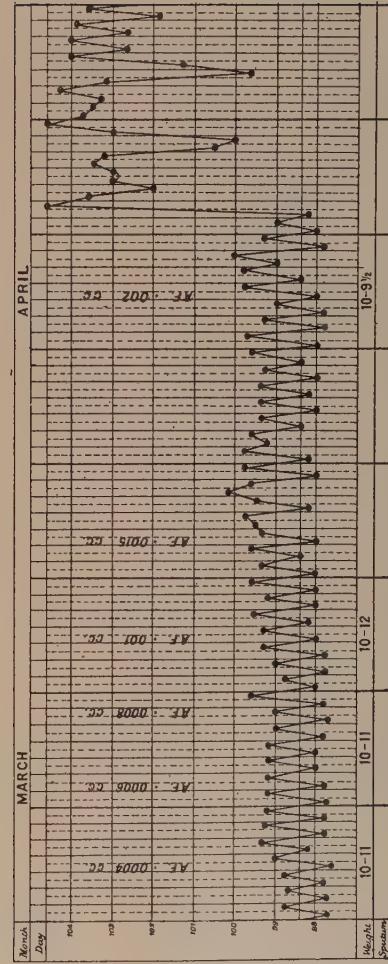
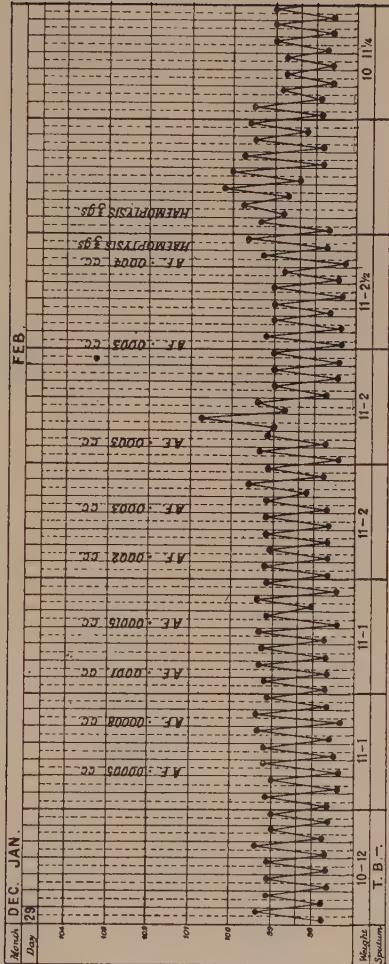


favourable. Tubercle bacilli disappeared from the sputum during the second month of treatment.

Tuberculin treatment was then begun with a dose of '00005 c.c. A.F. The first six inoculations produced no sign of a reaction, but following the seventh inoculation (of '0003 c.c.) there was a sharp rise of temperature to 100·8° F., and the normal level was not regained until after the lapse of 48 hours. A repetition of this dose 6 days later was well tolerated. On the day following the next inoculation, of '0004 c.c., a slight attack of haemoptysis ($\frac{1}{2}$ 3) occurred. Tuberculin was in consequence discontinued for 14 days. On the fourth day following the haemoptysis, all trace of blood disappeared from the sputum, and convalescence was fully established. On March 3rd tuberculin treatment was recommenced with a dose of '0006 c.c. This inoculation, and the next of '0008 c.c. on the 7th, did not give rise to reactions, but inoculations of '001 on March 12th and '0015 c.c. on March 18th were both followed by some unsteadiness of the temperature. On March 19th a slight pleural friction sound appeared in the left axilla. Tuberculin was again discontinued for 14 days. During this interval the rub disappeared and the temperature settled to its normal level. On April 2nd an inoculation of '002 c.c. was given, and on the two following days the temperature rose to 100°. On April 5th and 6th the temperature was normal, but on the 7th it rose to 105° F. This was the beginning of an acute relapse, characterised by rapid extension of the disease in the lower lobe of the left lung, and a pleural effusion at the right base. For the next 5 weeks the patient's temperature ranged from 101 to 104, and after a critical illness, which at one time seemed likely to prove fatal, a comparative degree of convalescence was slowly re-established.

It may be argued that an acute extension of disease may occur at any time in the course of pulmonary tuber-

CASE 17. CHART 12.



culosis, and that when tuberculin is given to a considerable number of patients it must inevitably happen that a relapse will sometimes occur in close association with a tuberculin inoculation, and may not necessarily be the result of it. This encouraging view is taken by one of my colleagues in respect of the case just described, but I find a difficulty in accepting it.

It is very unusual for acute pleuro-pneumonia to develop suddenly in a favourable case undergoing sanatorium treatment; indeed, throughout my experience, with the exception of the broncho-pneumonia which sometimes follows an haemoptysis, I cannot recall a single example. It must not be forgotten, also, that it was the occurrence of similar accidents in 1890 which convinced careful observers in this country of the dangers attending the administration of tuberculin in cases of pulmonary tuberculosis and led them to abandon its use.

SECTION VIII

The Difficulty of Avoiding Reactions

IT is sometimes said that it is possible to avoid reactions when giving tuberculin by the method described by Bandelier and Roepke: v. note p. 9.

Temperature Charts No. 13 and No. 14 illustrate how, without previous warning of any kind, a reaction may occur suddenly during a reactionless course in a patient fully convalescent and apparently doing well.

In the first case (Chart 13) the reaction occurred after 19 weeks of treatment without reaction, and the pyrexia thus caused did not subside for 4 weeks.

In the second case (Chart 14) the reaction also occurred after some weeks of treatment without any sign of reaction. In this latter case, however, all traces of the reaction cleared up in 24 hours.

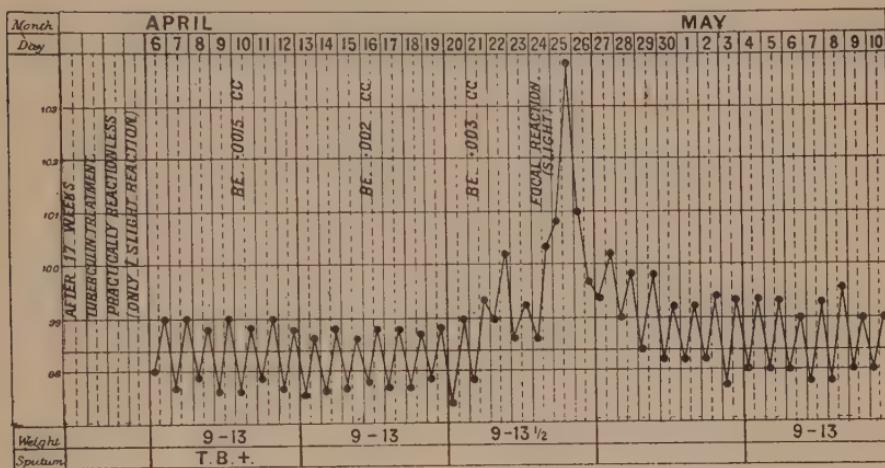
(a) Toxic Symptoms without Febrile Disturbance may indicate a Reaction

Apart from those which are characterised by a definite rise of temperature, there are various types of reactions which retard progress, and if they do not contra-indicate the treatment altogether, demand the greatest possible attention to dosage. The most important of all is a focal disturbance, increase of moist sounds in the diseased lung, or haemoptysis, which may occur independently of any febrile manifestation. Of far greater frequency is a vague feeling of malaise, which persists for

PRELIMINARY REPORT ON TUBERCULIN 45

some days. If, in the face of these symptoms, the treatment is persisted in, loss of appetite and loss of weight

CHART 13.

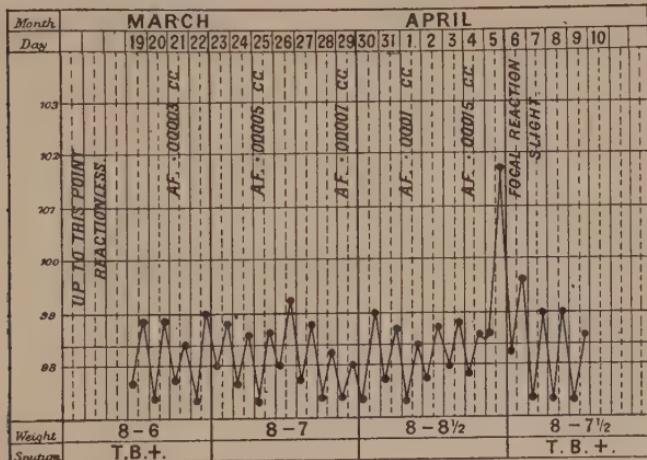


Exercise

8 Miles a day.

Bed.

CHART 14.

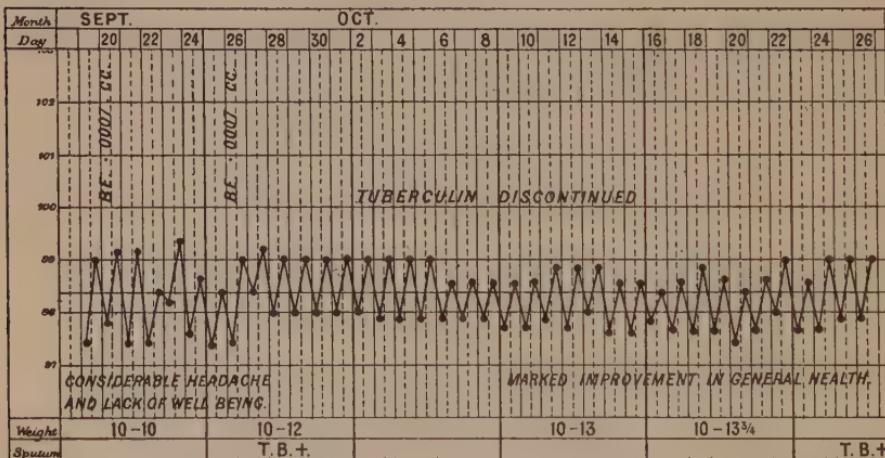
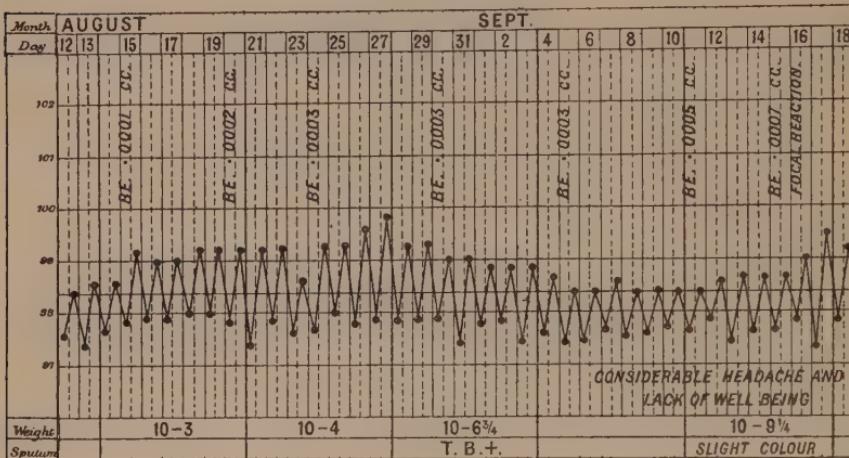


follow. Not infrequently in these cases there is nothing else to suggest any undue reaction, but the development

46 PRELIMINARY REPORT ON TUBERCULIN

of such a condition must be regarded as a reaction and so treated.

CASE 18. CHART 15.



CASE 18

Chart No. 15 well illustrates this condition.

PRELIMINARY REPORT ON TUBERCULIN 47

The case was one of moderately advanced disease, and, to judge by the temperature chart and the gain of weight, the patient appeared to be doing well. When a dose of '003 c.c. was reached, he began to suffer from malaise following each inoculation, and this persisted more or less throughout the intervals between the inoculations. No other unfavourable effect of the tuberculin was noticeable except for a slight focal reaction on one occasion. The toxic symptoms completely disappeared when tuberculin was discontinued, and the patient was at once able to resume exercise (which had been given up), much to the benefit of his general health.

SECTION IX

Tuberculin Injections in Febrile Cases

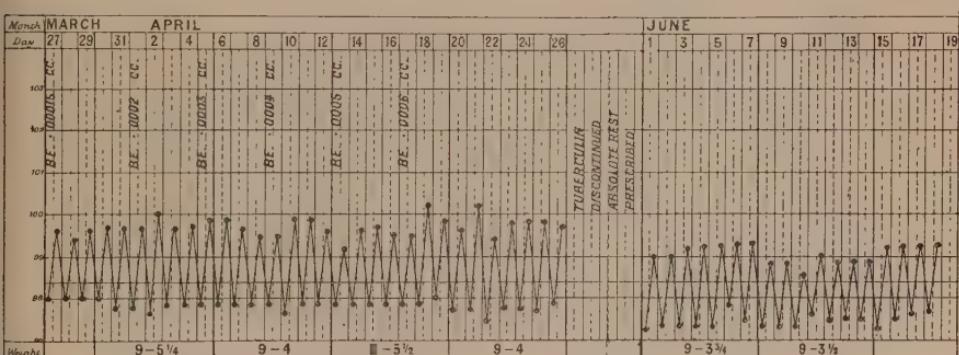
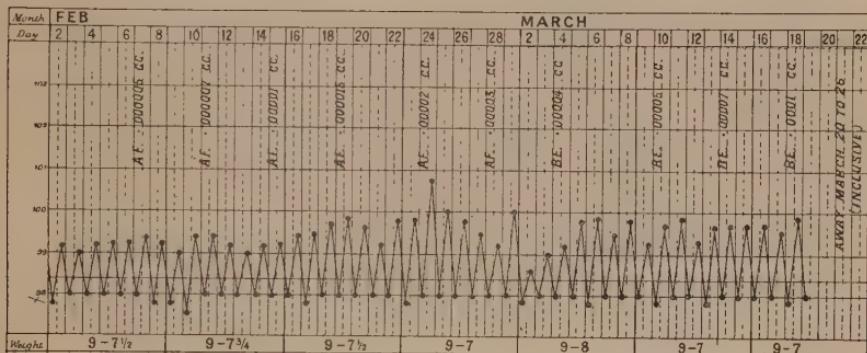
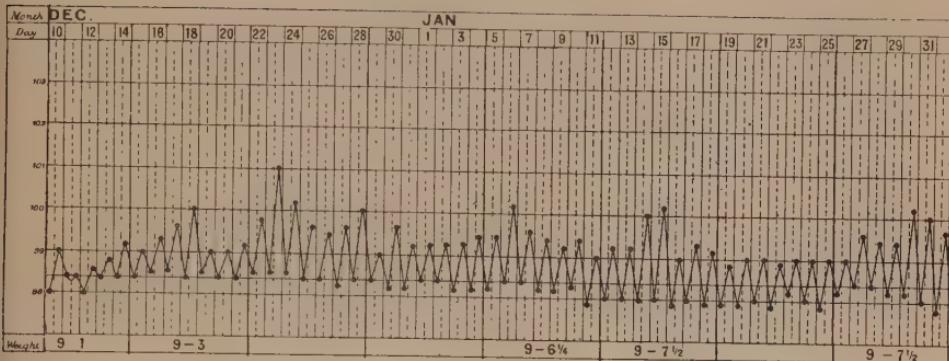
WE have received very little encouragement in the treatment of febrile cases with tuberculin, and have failed to obtain any conclusive evidence of the antipyretic value which some observers have claimed for it.

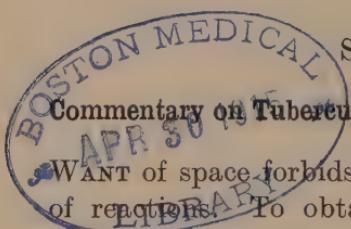
With care, tuberculin can often be given to febrile cases without the production of reactions, but even if such disturbances are avoided, no beneficial effects have so far been noticed.

CASE 19

The next Chart, No. 16, is that of a slightly febrile case, treated at first for 8 weeks on general lines, then for 11 weeks with tuberculin (reactionless course), and subsequently by complete rest without tuberculin. It will be seen that with absolute rest the patient's condition showed the most definite signs of improvement. The tuberculin did not appear to do any harm, but the patient said he felt distinctly better when it was discontinued, and of more importance still is the fact that the temperature fell to normal shortly after the injections were stopped.

CASE 19. CHART 16.





SECTION X

Commentary on Tuberculin Injections in Relation to Reactions

WANT of space forbids the giving of further illustrations of reactions. To obtain anything approaching a grasp of the varying degrees of intolerance to tuberculin that are met with, the conditions under which they develop, and their varied significance in different types of patient, a study of the records of a large number of cases is necessary.

In such a report as this, it is only possible to give a brief epitome of the impressions left by a critical review of this character.

It is quite clear that a "favourable case" of pulmonary tuberculosis—that is, a case, irrespective of its exact clinical type, which we know by experience should do well if given anything like a fair chance—can nearly always take tuberculin in steadily increasing doses without reactions through a complete course. There is little or no tendency to reactions, and when they occur they are usually transient in character. Only the careless can fail to immunise patients of this class to tuberculin. Bandelier and Roepke thus express a similar opinion:¹ "It is our experience that patients whose disease takes a conspicuously favourable course possess a natural raised resistance to tuberculin, and that it is just those patients who tolerate tuberculin well who progress favourably." With regard to the value of tuberculin in such cases, our experience appears to suggest that tubercle bacilli

¹ *Loc. cit.* p. 23.

are more quickly lost when tuberculin is given, our figures giving the percentage of cases in which T.B. have disappeared having risen somewhat since tuberculin treatment has been adopted. The patients treated with tuberculin have remained in the sanatorium longer than those who were treated on general lines only; the records for the two series of patients are therefore not comparable. This question is more fully dealt with in the section of this report which describes the results of tuberculin treatment.

On an average, some 30 to 40% of the patients in the sanatorium at any one time come within the definition of "favourable cases."

At the other end of the clinical scale are the least favourable cases, those which we feel instinctively will probably not do well. They are definitely febrile, or with a temperature which is unsteadied by the least exertion, with digestion and muscular system enfeebled and general lack of tone. Such cases are, in our experience, altogether unsuited for tuberculin, and we have never yet seen one of this character in the least degree benefited by it.

Between these two extremes represented by the favourable case and the frankly unfavourable case, there is a large group which is represented by some 30 to 40% of all the admissions to the sanatorium. Many of this intermediate class can with a little trouble be worked up to a fair degree of tolerance to tuberculin. More often than not, this is achieved at the expense of a certain number of slight reactions, each of which necessitates absolute rest for a few days. For everything in the nature of a reaction, however slight it may be, occurring in such cases, demands instant recognition in the shape of absolute rest until the effects of the reaction have completely passed off. It can be well understood that under these circumstances it is very easy to interfere with the

uniform rate of a patient's progress as judged, amongst other things, by the capacity to take gradually increased amounts of exercise, and this implies that the establishment of full convalescence is retarded. As a set-off against this, the patient has to his credit a varied degree of immunity to tuberculin. Whether such a degree of immunity is in the long run of service, is open to question.

All clinical experience is opposed to the provoking of any febrile disturbance in a case of pulmonary tuberculosis; in fact, of disturbing in any way the general well-being of the patient. Sanatorium treatment, which, in spite of its limitations, has done a great deal for consumptives, relies for success upon the restoration and maintenance of the patient's general health, by the systematic use of fresh air, rest, and exercise, and by the elimination of any factor which may tend in any way to lower it. On the other hand, any method of treatment which disregards these essentials is calculated to arouse our doubts, and there is no question at all that, except in the treatment of the more favourable cases, tuberculin as generally administered often upsets the even tenor of the patient's progress.

To quote again from Bandelier and Roepke,¹ these authors, in a chapter dealing with reactions, state that "the maxim, to remain as close as possible to the reaction limit, without well marked or severe reactions occurring, coincides with the experience that the most evident success has been obtained with slight reactions up to 100·4° F. or a little over. There is on theoretical grounds nothing to be said against this if proper precautions and supervision are observed, although the production of these slight reactions is by no means always attained." These opinions do not appear to me to be consistent with treatment without reactions, or, as I would put it, without disturbance of a patient's well-being.

¹ *Loc. cit.* p. 149.

It is not denied that a number of examples may be brought forward to show that reactions to 100·4° F., or even higher, *may* do no harm. Our own records prove this, but it is not to the point. So long as there is no evidence to prove that they are of any benefit, and a great deal of evidence to show that at any time they may do much harm, there can be no room even for discussion as to what is the correct practice.

The brief survey I have given of our experience in the administration of tuberculin will explain how it is that practitioners differ so much in their opinion as to the value of this form of treatment. A large number of medical practitioners have not the opportunity of seeing tuberculin given on a large scale, or of following many cases thus treated over a prolonged period. They try it tentatively on a few patients, and are probably much influenced by the first results they obtain. Those who are wise or fortunate in their earliest selections for the treatment will be favourably impressed; under opposite conditions an unfavourable verdict is as fully assured. Further experience commonly tends to modify either view, and the observer finally is left in doubt as to what his opinion really is.

SECTION XI

Methods of Tuberculin Treatment now in Use at the Sanatorium

AT the present time (June 1913), we are treating the favourable cases with tuberculin, and following a modification of the technique recommended by Bandelier and Roepke. We have satisfied ourselves that with reasonable care this modified method is a safe one for such cases since reactions can be avoided. All the less favourable cases we are treating upon general lines only, until such time as these measures have qualified them for inclusion amongst the more favourable. If sufficient improvement is not made, tuberculin is not given at all. A good working indication of the necessary degree of improvement is, in addition to gain of weight, diminution of symptoms, etc., a level temperature curve, in spite of daily exercise of some 4 to 6 miles. We recognise that this somewhat restricted use of tuberculin could in all probability be broadened without ill result, provided we could with certainty give to these less favourable cases an absolutely reactionless course.

This implies a modification in our methods of administration, and we shall shortly begin another series of observations, working more upon the principle of small doses with constant proportional increase. This work will be dealt with in a later report.

Additional Note, November 1913

We are now giving tuberculin in smaller amounts, the initial dose being a lower one than hitherto, and all subsequent doses on the same reduced level. There is in consequence much less tendency to reactions and to the associated instability of temperature and of general well-being. This allows of exercise being more freely permitted to our patients treated with tuberculin. A fair proportion of the cases thus treated now do heavy work in the gardens in the morning, and walk some 5 miles in the afternoon, except only on the days of inoculation. The curtailment of exercise which is necessary when tuberculin is administered in the larger doses is a distinct loss, and has resulted in our not having secured for our patients, during the past 18 months, the same high level of physical well-being as in former years. Further, by using the smaller doses, we are now experiencing less of the ill-results, such as febrile disturbances, attacks of pleurisy, etc., which have certainly occurred more frequently since tuberculin has been used.

Our present endeavour, in short, is again to give to our patients the full measure of treatment by increasing amounts of exercise, thus securing for them the proven advantages of the older methods, and in addition such advantages as may be derived from a reactionless course of tuberculin.

SECTION XII

The Effect of Tuberculin upon the Symptoms of Pulmonary Tuberculosis

(1) *Cough and Sputum*

THERE is very often a slight temporary increase of cough and sputum lasting for 24 hours after an inoculation. This is quite commonly met with from time to time, even in the apparently successful cases, and more especially so during the earlier stages of a course of tuberculin. This condition is probably due to a slight hyperæmia of the diseased areas, and is not in itself necessarily of unfavourable significance ; for a slight increase of sputum of this character, occurring in a patient who is obviously doing well, may be the precursor of a diminution in, and ultimate loss of, sputum.

(2) *Physical Signs*

Tuberculin often has a distinct effect upon the physical signs of the lung. Quite commonly there may be noted amongst cases treated with tuberculin a phenomenon rarely observed under any other method of treatment, namely, a definite increase in the area of physical signs occurring in a patient who is in every way making satisfactory progress. This condition is most likely to be met with in a case of incompletely arrested disease, presenting only slight physical signs, such as, for instance, impairment of resonance, alteration in breath-sounds, with perhaps a few crepitations on cough at the apex of one upper lobe, with slight loss of resonance at the apex of the lower lobe. After

some 6 weeks of seemingly reactionless tuberculin treatment in such a case, examination of the chest may show an extension of the area over which adventitious sounds are to be heard. They are now audible down to the third space in front, at the apex of the lower lobe, and for some 2 inches or so along the interlobar septum. These added sounds are always of a peculiar type, quite constant, and increased by or only audible during cough. Simultaneously with the increase of adventitious sounds, sputum may cease altogether, and every other available indication testifies to the excellent progress of the patient. The explanation offered is that the tuberculin, acting upon quiescent areas of disease, makes them capable of recognition just in the same way as diagnostic doses will often do, and that the newly developed sounds are indicative of increasing fibrosis resulting from the hyperæmia set up by the tuberculin.

It is impossible to speak with any degree of certainty on this point, and, as mentioned later, it may well be that these changes have a much less favourable significance.

To give an example: Mr. C was admitted into the sanatorium on August 4th, 1912, with physical signs suggesting arrested or obsolete disease at the right apex, and more recent disease in the upper third of the left upper lobe. There was no crepitation on cough at the right apex, but in the upper third of the left upper lobe there were a few fine crepitations. There were no obvious signs of disease, such as loss of resonance or alteration in breath-sounds, in the lower lobe of either lung. The patient's general condition was good, and he was afebrile. He had a very small amount of sputum in which bacilli were present.

He was given a practically reactionless course of B.E., beginning on August 10th and ending on November 14th. On September 2nd, the physical signs were unaltered, but on September 30th fine crepitations were audible on

cough in the upper third of the upper and lower lobes of the right lung, and at the apices of both lobes of the left lung. On October 28th, the report was as follows : Right lung.—Fine crepitations on cough to the third rib in front, also at the apex behind, and at the apex of the lower lobe. Left lung.—Fine crepitations on cough at the apices of both lobes. Health excellent. Sputum, occasional traces. No T.B. were found. On the patient's discharge in December, the physical signs remained unaltered, no T.B. were to be found, and recovery appeared to be complete. The patient then returned to his duties as postmaster in a country town, and so far his after-history has been quite satisfactory.

Most physicians are sceptical as to the favourable interpretation which is suggested above. They find it difficult to reconcile an increase of physical signs with progress towards recovery. However, to recognise this change as necessarily a prejudicial one is to forbid the risk of producing a focal reaction in a doubtful case by diagnostic inoculations, for the phenomena are identical. Many condemn the production of a focal reaction under any circumstances, and there is much to be said in support of their contention.

Returning to the subject of increased physical signs occurring in the course of tuberculin immunisation, there is one great practical difficulty that we have to deal with. Is it justifiable, after some 2 months' treatment, to revise the estimate originally made as to the extent of the lesion ? If not, it can only be recorded that the area of active disease has extended, which we may not believe to have happened. The possibility of the disease extending under tuberculin treatment, in the absence of any marked reactions, must be admitted.

Cases have occurred somewhat similar to the one I have just detailed, in which it has been impossible to say definitely whether or not the increase of signs indicated

some extension of the disease. To have any doubt on the point is very disquieting. My misgivings have not been lessened by the following two incidents, concerning which there is no room for doubt:

CASE 20

Development of Tuberculosis of the Larynx during a course of apparently successful Tuberculin Treatment

Miss A.—A typical early, favourable case, with bacilli in the sputum. On admission, there was slight loss of resonance at the apex only of the left lung, with no adventitious sounds. Of the larynx, Sir St. Clair Thomson recorded as follows: "Suspicious deposit in the left ventricular band and in front of the right arytenoid. No abrasion."

Examining the larynx 2 months later, Sir St. Clair Thomson passed it as normal.

In the meantime, a course of tuberculin had been commenced. A reactionless course was continued up to 2 c.c. A.F., and after a short interval a reactionless course of B.E. was given. The patient's progress appeared to be quite straightforward and satisfactory in every way. At the end of 16 weeks of tuberculin treatment, T.B. were no longer found, nor were they found again during the remaining 12 weeks of the patient's stay at the sanatorium.

Shortly after the disappearance of the bacilli from the sputum, the patient complained of irritation of the throat, and examination by Sir St. Clair Thomson showed the presence of a definite small ulcerated cone over the right arytenoid cartilage. Tuberculin was then discontinued. Six months later, this lesion was still present, although much reduced. The lung disease remained unchanged throughout.

CASE 21

Miss B.—A case of moderately advanced disease of recent origin. General condition favourable. Larynx, on admission in November 1911, examined by Sir St. Clair Thomson and pronounced to be normal.

Tuberculin treatment began on January 3rd, with .000005 c.c. A.F., was continued up to August, the final dose being .7 c.c. By this date T.B. had disappeared from the sputum, and except for one reappearance in January of the following year they were not found again. (The patient was discharged in March.) During the last week of the tuberculin treatment, examination of the larynx showed the development of a tuberculous deposit in the inter-arytenoid fold. This deposit for a time extended and then ulcerated. Treated with absolute vocal rest, and later by the galvano-cautery, it slowly cleared up, and in March 1913, eight months after the detection of the laryngeal disease, Sir St. Clair Thomson regarded the larynx as healed.¹ At this date the patient's general health was good, and although there were a fair number of adventitious sounds still audible in the diseased lung, there were only traces of sputum, and T.B. could not be found.

It is not of course intended to imply that tuberculin was responsible for the development of laryngeal tuberculosis in these two cases, but it will be observed that, coincident with the apparent arrest of the lung disease and loss of bacilli, in the one case there developed a focus of tuberculous disease in an area which had hitherto been sound, and in the other a slight lesion which had cleared up completely after the first few weeks of treatment, reappeared in an aggravated form, and subsequently improved very slowly.

¹ Since this report was written signs of active tuberculosis have reappeared in the larynx.

SECTION XIII

Mixed Infections

MY colleague, Dr. Radcliffe (*Parkes Weber Prize Essay*,¹ 1912), has shown that in sanatoria situated in the country a true secondary infection is rare, even in cases of advanced disease. So far as our work with tuberculin is concerned, the condition of mixed infection as a contraindication for tuberculin treatment is practically nonexistent. It is possible that this may not be the case in large cities. None the less, the fact of a patient doing badly on tuberculin is no evidence that a mixed infection exists. Some observers would appear to think that it is.

¹ *Zeitschrift für Tuberkulose*, October 1913.

SECTION XIV

Cases treated with Tuberculin after they had left Midhurst

By far the greater number of our cases treated with tuberculin have not continued this treatment after their discharge from the sanatorium. This is, in some ways, unfortunate, for it is desirable to obtain evidence of the effect of systematic and prolonged treatment by tuberculin in a large number of cases. It is contended that tolerance to tuberculin represents an immunisation to the toxins of the tubercle bacillus. If this view is correct, it would be to the advantage of the patient that such tox-immunity should be maintained for a long period, in fact until the disease is obsolete; for the tox-immunity with an associated development of antibodies should be a safeguard against relapse. Bandelier and Roepke¹ claim that in their experience tolerance to tuberculin confers this immunity, but Schröeder² holds an opposite opinion, namely, that relapses are frequently observed in highly immunised patients. This important question could be satisfactorily solved by the sanatorium with the co-operation of the general practitioner and tuberculin dispensaries. At the present time a small minority of our patients who have returned home are keeping up the inoculations, and of this number 20 patients are under the care of one physician, whose experience and caution can be relied

¹ *Loc. cit.* p. 280.

² Schröeder, *Beiträge z. Klinik d. Tuberk. v. spez. Tuberkulose Forschung*, Bd. xxii. Heft 1.

upon. This arrangement for after-treatment has in every case been made with the consent of the patient's medical attendant. There are already indications that tuberculin, when it suits a patient, should be given for a long time, and that failing this, and also in spite of this continued treatment, we must be prepared for disappointments.

Reappearance of T.B. in Sputum

The following are the after-histories of 3 of the cases treated with tuberculin which left the sanatorium with their sputa clear of T.B.

CASE 22

Mr. A. Age 24 years. Admitted May 18th, 1912.

His history was only of some 6 weeks' duration, namely, a cold followed by haemoptysis. T.B. were found in the blood of the haemoptysis, but were not found later.

On admission, there were no definite physical signs. The general condition was good, and the body-weight and temperature were normal. There were only traces of sputum, and T.B. were not found at any time during the patient's stay in the sanatorium. The case was probably one of early disease, in a quiescent or arrested condition. The patient was given a course of B.E., beginning with .00001 c.c., and finishing with .1 c.c. The course was reactionless throughout, and the patient was able to take the full amount of exercise prescribed at the sanatorium. On discharge, after 5 months' treatment, the patient appeared to be quite well, and after a short holiday, he returned to work as an insurance clerk. Five months later, he "caught a cold," sputum returned, and T.B. were found. He was then readmitted. The physical signs were still rather indefinite, but there was some perceptible loss of resonance at the left apex.

64 PRELIMINARY REPORT ON TUBERCULIN

The general health was excellent, body-weight was satisfactory, and temperature normal. The patient is now having a second course of tuberculin, and up to the present date (after 14 weeks' treatment), T.B. are still present.

CASE 23

Miss L was admitted October 1911 with a history of some 3 months' duration. On admission, there were signs of disease at the apices of both lobes of the left lung, and at the apex of the right lung. The general condition was favourable, and the body-weight and temperature were normal. In addition to the disease of the lung there was slight tuberculous disease of the larynx (ulcer in front of left arytenoid and congestion of posterior third of the left vocal cord). Sputum contained T.B.

When thoroughly convalescent as the result of 13 weeks' general treatment, T.B. were still to be found in the sputum. Tuberculin treatment was then (December 31st, 1911) begun, with '000005 c.c., and ended on August 7th with a final dose of 1 c.c. In all, the tuberculin course lasted 33 weeks, 44 inoculations being given. The patient was discharged in August 1912, after 10 months in the sanatorium, apparently quite well, and T.B. had not been found for $4\frac{1}{2}$ months. She then left the sanatorium to resume life under almost ideal conditions in the country. Six months later there was a recurrence of the disease in the left lung, cough returned, and tubercle bacilli reappeared in the sputum.

CASE 24

Miss M, when admitted in October 1911, had evidence of early disease at the apices of both lungs. The general condition was good and the temperature normal.

PRELIMINARY REPORT ON TUBERCULIN 65

There were only occasional traces of sputum, which contained T.B. After 11 weeks' general treatment, the patient was apparently well, except for the fact that the traces of sputum coughed up once or twice a week still contained bacilli. Tuberculin treatment was then begun. A course of A.F. was followed by a course of B.E., in all 38 inoculations being given during a period of 32 weeks. On discharge in August 1912, after 10 months' treatment in the sanatorium, the patient appeared to have made a complete recovery, and T.B. had not been found for 12 weeks. She then returned to clerical work under exceptionally good conditions in a country convalescent home. Eight months later the disease again became active in both lungs, and bacilli reappeared in the sputum.

The After-Histories of 42 Cases from whose Sputum T.B. Disappeared

The following are brief notes as to the after-histories up till November 1913 of the 42 patients from whose sputum T.B. disappeared after treatment in the sanatorium with tuberculin. Particular attention has been directed to the following points : (a) whether or not the tuberculin inoculations were continued after the discharge of each patient from the sanatorium, and (b) whether the bacilli have or have not reappeared in the sputum.

THE FOLLOWING THIRTY CASES HAVE NOT CONTINUED TUBERCULIN TREATMENT SINCE LEAVING MIDHURST

Date of Discharge.	Report November 1913.	Result of Examination of Sputum.
April 1912 . . .	Well and at work	T.B. present
May 1912 . . .	” ” ”	T.B. ”
June 1912 . . .	Health fair; at work	T.B. ”
June 1912 . . .	Well and at work	T.B. absent
June 1912 . . .	” ” ”	T.B. ”
June 1912 . . .	” ” ”	T.B. ”
June 1912 . . .	” ” ”	T.B. present

66 PRELIMINARY REPORT ON TUBERCULIN

Date of Discharge.	Report November 1913.	Result of Examination of Sputum.
Aug. 1912 . .	Well and at work	T.B. absent
Sept. 1912 . .	," " "	T.B. "
Oct. 1912 . .	," " "	T.B. "
Dec. 1912 . .	Died Oct. 17th, 1913	T.B. found in October
Dec. 1912 . .	Well and at work	T.B. absent
Feb. 1913 . .	," " "	T.B. "
Feb. 1913 . .	Health fair; at work	T.B. present
Feb. 1913 . .	Relapsed	T.B. "
April 1913 . .	Health fair	T.B. "
Aug. 1912 . .	Relapsed	T.B. "
Dec. 1912 . .	Well " and at work	T.B. "
Dec. 1912 . .	Relapsed	T.B. absent
Aug. 1912 . .	Well (in Australia)	T.B. present.
Feb. 1913 . .	Well and at work (in Australia)	No record
Oct. 1912 . .	Well	," "
March 1913 . .	Lungs well: now suffering from melancholia	T.B. absent
Sept. 1912 . .	Health good: had slight haemoptysis in Jan. 1913	T.B. present
March 1913 . .	Relapsed	T.B. "
Dec. 1912 . .	Well and at work	T.B. absent
June 1912 . .	Health good	T.B. present
June 1912 . .	Well and at work	T.B. absent
Nov. 1912 . .	Relapsed	T.B. present
July 1912 . .	Well	T.B. present

THE FOLLOWING NINE CASES HAVE CONTINUED TUBERCULIN TREATMENT SINCE DISCHARGE

Date of Discharge.	Report November 1913.	Result of Sputum Examination.
March 1912 . .	Well and at work	T.B. absent
June 1912 . .	," " "	T.B. "
Jan. 1913 . .	Well " "	T.B. "
Oct. 1912 . .	Well and at work	T.B. "
May 1913 . .	," " "	T.B. "
April 1913 . .	," " "	T.B. "
March 1913 . .	Well " "	T.B. present
March 1913 . .	Health fair only	T.B. "
Nov. 1911 . .	Well and at work	T.B. "

Three cases have been lost sight of.

SECTION XV

General Results in Cases Treated with Tuberculin in Addition to the Methods of Treatment usually carried out at the Sanatorium

So far as sanatorium practice is concerned, there is probably no better method of arriving at a correct estimate of the value of tuberculin in sanatorium treatment than to compare the results obtained in two similar series of patients, as nearly as possible under the same conditions, the one treated with tuberculin, the other on general lines alone.

This we are enabled to do. The King Edward VII Sanatorium is fortunate in possessing a valuable control, in the shape of the records of a large number of patients treated without tuberculin. These records, dating from the opening of the Institution (1906), have been kept in a uniform manner, so that the element of personal equation in such matters as classification on admission and on discharge, judgment of progress made, etc., has also been constant, one individual having been responsible for the records throughout. The same remarks apply to the observations on tuberculin, for the work of the sanatorium since October 1911 has been carried on in all respects as in previous years, the only new element being the use of tuberculin.

Method Adopted for Recording the Results

The methods of classification of patients on admission and on discharge which have been used in the preparation of all the Annual Reports have been adopted.

68 PRELIMINARY REPORT ON TUBERCULIN

This classification (Turban-Gerhardt), described in the official journal of the International Tuberculosis Committee, is substantially as follows :

Group 1.—Disease of slight severity, limited to small areas of one lobe on either side, and which, in case of infection of both apices, does not extend beyond the spine of scapula or the clavicle, or in case of affection of the apex of one lung does not extend below the second rib in front.

Group 2.—Disease of slight severity, more extensive than 1, but affecting, at most, the whole of one lobe; or severe disease, extending at most to the half of one lobe.

Group 3.—All cases of greater severity than group 2, and all those with considerable cavities.

By disease of slight severity is to be understood : disseminated foci characterised by slight dulness, indefinite rough or weak vesicular, vesico-bronchial, or broncho-vesicular breathing, and fine and medium râles.

By severe disease : massive infiltration recognised by definite dulness, broncho-vesicular or bronchial breathing, with or without râles.

Cases with signs of considerable cavities, giving rise to tympanitic percussion with amphoric or cavernous breathing, and numerous coarse consonating râles, come under group 3.

Pleuritic dulness, if only of slight extent, is to be left out of account ; if it is considerable, pleuritis should be specially mentioned under tuberculous complications.

The following terms are used to describe the conditions of patients on discharge from the sanatorium :

“Disease arrested” : General health completely restored in every respect without any sign of disease of lung except such as is compatible with a completely healed lesion. Sputum, if still existing, free from tubercle bacilli.

“Much improved” : General health good. Physical signs in the lungs, though much diminished, not entirely

cleared up, *e.g.* perhaps limited to a few crepitations on cough only. Tubercle bacilli still to be detected in the sputum.

“Improved”: General health improved, but imperfectly restored. Physical signs of disease in the lungs, though less marked than on admission, still present.

“Stationary”: No appreciable improvement in the condition of the lungs or in general health.

“Worse”: General or local condition, worse.

Only one modification has been made in this report, *viz.* that the cases in which tubercle bacilli were found in the sputum, and those in which tubercle bacilli were not found, have been considered separately.

The records of King Edward VII Sanatorium show that the prognosis of these two classes of cases differ so widely that to consider them together is to introduce a serious source of fallacy. The evidence in proof of this is that, whereas of the patients diagnosed as suffering from pulmonary tuberculosis, but in whom the presence of tubercle bacilli could not be demonstrated, 89% were well and alive some years after their discharge, only 57% of those in whose sputum tubercle bacilli were found were so reported after a like interval of time. The difficulty of making a correct diagnosis, in the absence of T.B., is responsible for some of this disparity, and there can be little doubt that all statistics which deal with a large number of cases in which “T.B. were never found” include cases of early disease, cases of arrested and obsolete disease, and cases which have never had the disease at all.

In the various appendices to this report, some further information has been given as to the condition of the patients treated with tuberculin on admission and on discharge. For the sake of brevity, reference has been only made to the most essential points, *viz.* on

admission,—the presence or absence of fever and the relation of the body-weight to the average normal weight when in health ; and on discharge, the condition of the lung, the amount of exercise that could be taken, the relation of the weight to the normal weight, and the persistence or disappearance of T.B. from the sputum. The amount of exercise that can be taken is a good index of the capacity for work ; since for a patient to leave the sanatorium who has been walking 6 to 10 miles a day, is good evidence that he is afebrile and that in a large measure his general health is restored. Discharge with a body-weight equal to or a little above the normal points, too, in the same direction. Compared with these facts, especially when the presence or absence of bacilli is also recorded, information as to precise alterations in physical signs is of much less value as an indication of the patient's condition.

To this clinical information a note in each case has been added as to the total length of stay in the sanatorium, the number of weeks of tuberculin treatment, the variety of tuberculin used, and the number of inoculations given.

In these records are included all patients to whom tuberculin was given, whether they proved suitable or unsuitable for the treatment. In a sense the unsuitable may be said not to have been treated with tuberculin, but it must be remembered that tuberculin was tried, but without benefit.

SECTION XVI

General Results in 154 Cases treated with Tuberculin at Midhurst between October 1911 and May 1913

DURING the 19 months from October 1911 to May 1913, tuberculin was given to 154 patients; T.B. were found in the sputum of 130 (84.4%), and were not found in the sputum of the remaining 24.

These 154 cases may be classified as follows:

1. Cases in which Pulmonary Tuberculosis was believed to exist, though the presence of T.B. could not be demonstrated in the sputum	24
2. Definite cases of Pulmonary Tuberculosis (T.B. being present):	
a. Cases of early disease, Group 1	22
b. Cases of moderately advanced disease, Group 2	81
c. Cases of advanced disease, Group 3	27
Total	<u>154</u>

(a) Records of 24 Cases in which Tuberclle Bacilli were not found in the Sputum

Particulars with regard to these 24 cases are given in Appendix I. They have been divided into two groups, consisting respectively of 11 cases which gave a focal reaction in the lung to diagnostic doses of tuberculin (these 11 cases were considered to be suffering from

72 PRELIMINARY REPORT ON TUBERCULIN

recently active disease), and 13 cases which were not subjected to the tuberculin test. In 3 of this latter group tubercle bacilli had been found at some time previous to their admission to the sanatorium, and of the others 2 had recently suffered from characteristic haemoptysis.

These 24 patients all did well, as evidenced by the disappearance of symptoms, restoration of general health, and capacity for work, the only criteria by which we were able to estimate their improvement. In the absence of definite physical signs, or of anything more pronounced than some impairment of resonance and alteration of breath-sounds, it is impossible to say much as to the progress of the pulmonary lesion, except that such physical signs as did exist cleared up satisfactorily.

It is difficult to decide how best to classify these 24 cases on their discharge. There is precedent for recording them as on admission presenting signs of early disease, and on discharge of arrested disease, a method which gives the encouraging result of (approximately) 100% complete recoveries.

Statistical records of this character are clearly of no value, and are calculated to retard rather than to promote our knowledge of the true value of tuberculin.

These so-called early cases do very well under ordinary sanatorium treatment, it being unusual for such patients to fail to make an apparently complete recovery. The "after-history" records of King Edward VII Sanatorium show also that it is an unusual occurrence for such patients to relapse after receiving a course of sanatorium treatment and education.

The treatment of these cases, therefore, though doubtless of value to the individual patients and of interest in other respects, furnishes us with no useful information as to the value of tuberculin. All that can rightly be said is that such cases do just as well on sanatorium

PRELIMINARY REPORT ON TUBERCULIN 73

treatment with tuberculin as on sanatorium treatment alone.

(b) *Records of 130 Cases in which T.B. were present in the Sputum*

In the Appendices to this report are set out the full details of the treatment of the 130 patients in whose sputum tubercle bacilli were found. A brief summary of these data is given below :

- (a) As they deal with the general clinical results and
- (b) The effect upon the sputum as regards persistence or disappearance of T.B.

The general clinical result on discharge is expressed in terms which have already been defined. The T.B. records are perhaps of greater value, since the disappearance of T.B. from the sputum is an objective fact as to which, assuming that proper care is taken in the examinations, there cannot be any doubt, nor is it merely a matter of opinion. Until the lapse of time furnishes us with after-histories, no better data are available than those now given upon which to judge the progress of the cases treated with tuberculin.

The summaries are as follows :

Results of treatment of 130 Cases in the Sputum of which T.B. were found

TABLE I.—GENERAL RESULTS

	Arrested or much Improved.	Improved.	Stationary or Worse.
Group I., 22 cases	21 = 95·4%		1 = 4·6%
II., 81 cases	57 = 70·3%	11 = 13·5%	13 = 16·2%
,, III., 27 cases	6 = 22·2%	12 = 44·4%	9 = 33·3%
All cases together, 130	84 = 64·6%	23 = 17·7%	23 = 17·7%

N.B.—For classification of cases v. p. 68.

74 PRELIMINARY REPORT ON TUBERCULIN

TABLE II.—PERSISTENCE OR DISAPPEARANCE OF T.B. FROM SPUTUM

	No. of Cases Treated.	Lost Tubercl Bacilli.
Group I.	22	13 = 59%
," II.	81	27 = 33·3%
," III.	27	2 = 7·4%
All cases together . . .	130	42 = 32·3%

The general results, as the table shows, may be considered satisfactory. Of 130 cases treated, 64·6% left with their disease arrested or much improved, and with general health restored, 17·7% were discharged improved, and 17·7% failed to derive any benefit. These records are better than any the sanatorium has yet published.

Effect upon the Sputum

The disappearance, too, of T.B. from the sputum in 32·3% of the cases is also an improvement upon any of our previous results. They are not, however, as good as those published by other observers.

(c) The Fallacy of Selection of Cases

The fallacy of selection of cases must now be considered. Our own records represent the results of treatment of 130 cases, the great majority of which were selected as being suitable for treatment by tuberculin from amongst all those admitted to the sanatorium. The exceptions to this rule consist of a few patients with advanced disease, who were given tuberculin as a last resource. The actual proportion of tuberculin-treated patients amounted to 62% of all cases treated in the sanatorium during the period now under notice.

At one time the proportion of cases treated with tuberculin was higher, viz. about 70%. With increasing experience, the tendency has been to reduce this proportion; it now stands at about 40%.

The degree of selection exercised introduces a difficulty in estimating the success of our work, since we have no record of the results in similarly selected cases treated by sanatorium methods alone. There is no doubt that if the rules governing the selection of patients for admission to the sanatorium were made more strict, so that the 30 or 40% of less favourable cases now admitted were eliminated, the results of treatment would at once show a sensible improvement on any which we have hitherto published.

All that can be said is that the results of our tuberculin-treated cases, as shown by the tables, are satisfactory ; but whether or no these particular cases would have done as well without tuberculin, the records in themselves give no information.

SECTION XVII

A Comparison of Cases treated in the Sanatorium with and without Tuberculin

THE only method available for making a comparison between the results of cases treated with and without tuberculin, is to set out the general results obtained for the whole of the sanatorium before tuberculin was used, side by side with similar results obtained since its introduction.

This gives a view of the effect upon the general results by the introduction of some 60% of selected cases which were treated with tuberculin. It also shows to what extent those results are modified by the inclusion of the unselected patients treated without tuberculin.

It may be urged that it is misleading to include in the results of "tuberculin treatment" records of some 30-40% of cases which were unsuited for and did not receive this form of treatment. This may be so, but if the object is to ascertain the effect on the general results of the sanatorium of the use of tuberculin, no other method seems available.

In the following tables there have been set out, for purposes of comparison, the general results, and the results of the examination of the sputum under the two conditions stated :

1. In 606 consecutive cases treated in the sanatorium without tuberculin, 1908-1911.

2. In the treatment of all cases resident in the sana-

PRELIMINARY REPORT ON TUBERCULIN 77

atorium during 14 months of the period during which tuberculin has been largely used.

3. In the treatment of 130 selected cases treated with tuberculin.

The fact should be again emphasised that all these records refer exclusively to patients with tubercle bacilli in their sputum.

(a) Comparison of General Results

1. Results in 606 consecutive unselected patients (T.B. +) treated on sanatorium methods alone, 1908-11

	Arrested or Much Improved.	Improved.	Stationary or Worse.
Group I., 137 cases .	84·6%	8·7%	6·5%
Group II., 300 cases .	56·6%	21·0%	22·3%
Group III., 169 cases .	18·3%	37·8%	43·7%
Total, 606 cases . . .	52·3%	22·9%	24·7%

2. Results in 172 consecutive unselected patients (T.B. +) during 14 months—March 1912 to May 1913—of whom 111, or 64·5%, received tuberculin

	Arrested or Much Improved. ¹	Improved.	Stationary or Worse.
Group I., 25 cases .	84%	nil	16%
Group II., 110 cases .	55·4%	21·8%	22·7%
Group III., 37 cases .	18·9%	27%	54%
Total, 172 cases . . .	51·7%	19·7%	28·4%

¹ For "Groups" and definition of terms "Arrested," etc., see p. 68.

3. *Results in 130 (for the most part) selected cases (T.B. +) from November 1911 to May 1913, treated with tuberculin*

	Arrested or Much Improved.	Improved.	Stationary or Worse.
Group I., 22 cases . .	95.4%	—	4.6%
Group II., 81 cases . .	70.3%	13.5%	16.2%
Group III., 27 cases . .	22.2%	44.4%	33.3%
Total, 130 cases . .	64.6%	17.6%	17.6%

(b) *Comparison of Results as Estimated by the Disappearance or Non-disappearance of T.B. from the Sputum*1. *Results in 606 consecutive unselected cases (T.B. +) on sanatorium methods alone*

Lost T.B. whilst in sanatorium, Group I. . .	32.7%
" " " " " Group II. . .	15.3%
" " " " " Group III. . .	1.1%
All cases together	<u>15.3%</u>

2. *Results in 172 consecutive unselected cases (T.B. +), of which 64.5% (111) were treated with tuberculin*

Lost T.B. whilst in sanatorium, Group I. . .	49.6%
" " " " " Group II. . .	25.6%
" " " " " Group III. . .	8.3%
All cases together	<u>25.5%</u>

3. *Results in 130 selected cases (T.B. +) treated with tuberculin*

Lost T.B. whilst in sanatorium, Group I. . .	59.0%
" " " " " Group II. . .	33.3%
" " " " " Group III. . .	7.4%
All cases together	<u>32.3%</u>

SECTION XVIII

Commentary on the Foregoing Statement of Results

IN a paper recently presented to the Royal Society of Medicine upon the results obtained at the sanatorium during the four years 1907-1911, a period during which tuberculin was not used, I stated that in my opinion, if tuberculin is a potent additional factor for good, we at King Edward VII Sanatorium, after the introduction of tuberculin, should find evidence of its value in a higher proportion of patients discharged with sputum free from bacilli, and a lower mortality year by year as shown by their after-histories. It was also pointed out that it was not so much to the cases which had no T.B., nor to the early cases with T.B., nor again to the advanced cases, that we should look for this evidence, since the two former do so well without tuberculin, whilst for the latter little can be hoped, but rather to the large number of cases of moderately advanced disease, classified in sanatorium statistics under Group 2.

In an Interim Memorandum upon my impressions on the tuberculin treatment at the sanatorium, presented to the Council early in 1913, and written before this report was commenced, I stated that "so far as the general progress of the cases is concerned, namely, in respect to gain of weight, variation in temperature, alleviation of symptoms, improvement in general appearance, etc., no difference can be seen between patients treated with or without tuberculin. Excluding the

hint given now and again by the slight but typical rise of temperature which often follows a tuberculin injection, it did not seem possible to differentiate, by observation of the general clinical progress, between a series of cases treated with tuberculin and a series treated on the usual sanatorium lines alone. Sir St. Clair Thomson expresses a similar opinion with regard to the cases of laryngeal tuberculosis."

The various records which I have just tabulated tend to confirm the impressions given in this Interim Memorandum. Admitting the difference in the total number of cases dealt with, the records of all cases during the pre-tuberculin years, and for the period of 14 months during which tuberculin was used (*i.e.* sections 1 and 2 of each table), are strikingly similar. They indicate that the use of tuberculin has had no appreciable effect upon the general results.

It is desirable that every available means be utilised to check the figures just given. Sir James K. Fowler has suggested the following control observation, to eliminate the fallacy of selection; namely—

1. To select from the cases treated with tuberculin all those whose condition seems favourable, excluding those in which, after the failure of other methods, tuberculin was given in the hope rather than in the expectation that it might do good.

2. To select an equal or larger number of cases from amongst those treated on ordinary sanatorium lines before tuberculin was used; the basis of selection being an affirmative answer to the following question: "If this patient were admitted now, would he be regarded as a suitable case for tuberculin treatment?"

3. To compare (1) with (2) as regards (a) the general result as shown by the condition on discharge; (b) the result of examination of sputum for T.B.

This comparison can be readily made, since, in the

PRELIMINARY REPORT ON TUBERCULIN 81

consecutive annual reports of the sanatorium, the condition of every patient discharged during the year is set out in full detail, note being specifically made as to whether each case was a favourable or an unfavourable one.

I have then extracted from the annual reports for 1908-9 and 1909-10, respectively, the records of 147 consecutive patients, whose conditions are stated to have been favourable; and to make the various records as far as possible comparable, I have included in each group the same number of patients as are included in the series of cases treated with tuberculin, namely, 25 in Group 1, 102 in Group 2, and 20 cases in Group 3.

The results are as follows :

GENERAL RESULTS IN

*147 Consecutive Favourable Cases (T.B. +) treated with Tuberculin
1912-13*

Group.	No. of Cases.	Arrested.	Much Improved.	Improved.	Stationary or Worse.
1	25	15	8	1	1
2	102	30	43	14	15
3	20	2	9	6	3
Total	147	47	60	21	19

*147 Consecutive Favourable Cases (T.B. +) (1908-9) treated without
Tuberculin*

Group.	No. of Cases.	Arrested.	Much Improved.	Improved.	Stationary or Worse.
1	25	12	11	2	—
2	102	16	54	23	9
3	20	—	10	7	3
Total	147	28	75	32	12

147 *Consecutive Favourable Cases (T.B. +) (1909-10) treated without Tuberculin*

Group.	No. of Cases.	Arrested.	Much Improved.	Improved.	Stationary or Worse.
1	25	10	12	2	1
2	102	22	50	12	18
3	20	—	9	8	3
Total	147	32	71	22	22

EXAMINATION OF SPUTUM IN

147 *Consecutive Favourable Cases (T.B. +) treated with Tuberculin (1912-13)*

		No. of Cases	Lost T.B.
Group 1	.	25	15
Group 2	.	102	30
Group 3	.	20	2
		—	—
		147	47
		—	—

147 *Consecutive Favourable Cases (T.B. +) treated without Tuberculin (1908-9)*

Group 1	.	25	12
Group 2	.	102	16
Group 3	.	20	0
		—	—
		147	28
		—	—

147 *Consecutive Favourable Cases (T.B. +) treated without Tuberculin (1909-10)*

Group 1	.	25	10
Group 2	.	102	22
Group 3	.	20	0
		—	—
		147	32
		—	—

A comparison of these tables shows that the results in the cases treated both with and without tuberculin are practically identical, with the exception that in the tuberculin-treated a higher proportion lost their T.B. and could thus be described as "arrested." The effect of this is to reduce somewhat the number classed as "much improved," with a corresponding increase in the number placed in the "arrested" class. This is well seen if we group together for each series (a) the "arrested" and the "much improved," and (b) the "improved" and "stationary or worse."

	(a) Arrested and Much Improved.	(b) Improved and Stationary or Worse.	Total.
Treated <i>with</i> tuberculin	107	40	147
„ <i>without</i> tuberculin 1908-09 :	103	42	147
„ „ tuberculin 1909-10 :	103	44	147

These results all show a slight advantage in favour of tuberculin, as shown by the fact that a rather larger number of cases which had been treated with tuberculin lost the T.B. from the sputum, but the fallacy introduced by the increased length of treatment of the tuberculin-treated cases must be allowed for.

This source of fallacy is a serious one, and it is possible that further analysis will show that the improvement in the records is entirely to be accounted for by the factor of increased length of treatment.

Still another method remains by which these results may be checked, namely, to set out the figures for loss of T.B. in all cases for each successive year from 1908 to 1913.

During the years 1908-9, 1909-10, and 1910-11, no tuberculin was given; in the year 1911-12 tuberculin was given to 15%, and in the year 1912-13 to 74.5% of the

patients. If tuberculin has had the beneficial effect indicated by the other methods of comparison, it should be possible to recognise it in an improvement of the results for the year 1912-13, as compared with those for the previous years.

The following are the records thus tabulated (I have also included in this table the average length of stay of the patients during each of the years dealt with):

TABLE SHOWING AVERAGE LENGTH OF STAY IN SANATORIUM OF ALL T.B. + CASES, AND THE NUMBERS WHO LOST T.B. BEFORE DISCHARGE.

Group.	Number of Cases.	Average Length of Stay.	Lost T.B.	Percentage.	Year.
		Weeks.			1908-09
I : :	35	18.9	15	42.8	
II : :	98	20.2	19	19.4	
III : :	82	14.4	2	2.4	
All cases .	215	17.8	36	16.7	
					1909-10
I : :	48	17.2	15	13.2	
II : :	96	19.1	13	13.5	
III : :	48	16.5	nil.	nil.	
All cases .	192	17.9	28	14.5	
					1910-11
I : :	54	18.7	15	27.7	
II : :	106	19	14	13.2	
III : :	39	15.3	nil.	nil.	
All cases .	199	18.2	29	14.5	
		Treated with Tuberculin.			1911-12
I : :	40	9	16.8	19	
II : :	114	22	18.8	22	
III : :	46	1	13.8	2	
All cases .	200	32	17	43	
					1912-13
I : :	17	17	24.7	9	
II : :	101	80	24	24	
III : :	43	23	17.5	3	
All cases .	161	120	21.7	36	

It should be stated that in preparing these statistics I have not considered as positive those cases in which T.B. were found shortly before admission, but in which we failed to demonstrate their presence. Many of these cases were undoubtedly positive, but their T.B. having disappeared before the date of admission to the sanatorium, they cannot be said to have lost them as a result of their treatment there.

It will be seen from the tables that the number of positive cases dealt with each year has remained very constant up till last year, when it fell appreciably, with the result that the average period of residence in the sanatorium was longer than it had been previously.

The figures for loss of T.B. also varied but slightly during the three years in which tuberculin was not given, being 16.7%, 14.5%, and 14.5%. In the following year, coincident with the first use of tuberculin, the figures rose to 21.5%, and during the past year they have improved further to 22.3%.

At first sight these results would seem distinctly to favour the use of tuberculin, but a closer analysis shows that the evidence to this effect is not so convincing as the figures suggest.

The year 1911-12, the records for which show a material improvement on those of previous years, was, as already stated, the year in which tuberculin was first given, but it was only in the last few months of the year that this new factor was introduced, and, all told, only 15% of the cases received tuberculin during the twelve months in question. It would seem improbable that this restricted use of tuberculin should have had the effect of improving the figures among the number of cases which lost their T.B. from 14.5% in the two preceding years to 21.5%, but should this in fact have been the case, we should expect to see a further marked improvement in the results, following a more general use of tuberculin in

the next year. This we do not find, the improvement being less than 1%, namely from 21.5% to 22.3%. It seems clear, therefore, that we have to look for some other factor which was operating favourably throughout the year 1911-12. It is at least certain that some of the improvement in this year is to be accounted for in the following way. At the end of 1910-11, the Ellermann and Erlandsen method of examining sputum was first used. By this method we obtain a positive result in some 30 to 40% of patients whose sputum is negative to repeated examinations by the ordinary method (for details, see page 67, *Annual Report*,¹ 1911-12). This means that since the adoption of the "E. and E." method as a routine means of diagnosis, failing a positive result by ordinary methods, some 30 to 40% of the cases which in former years would have been excluded from our records of positive cases have been included as such. This in itself would not be of great moment, were it not for the fact that these cases, negative to ordinary methods, and positive, perhaps, on one occasion only by the E. and E. method, readily lose their bacilli altogether, and often after a few weeks' treatment have no sputum for further examination.

To make these cases, which throughout their whole treatment are positive by the E. and E. method only, comparable with the cases which are positive by the older method, it is necessary that their sputum should also be examined by the improved method, on completion of their treatment. When possible this was done, but often, as previously stated, no such examination was possible. Not infrequently, however, after the establishment of the diagnosis by the E. and E. method, T.B. are found later by ordinary methods. Again, if the sputum of a patient on discharge is negative by ordinary methods and positive only by the E. and E. examination,

¹ See Section 1 of this report, page 2.

to make all the records comparable, the sputum should be regarded as negative and the patient recorded as having lost T.B. This possible source of fallacy, however, has only to be reckoned with in the year 1910-11.

The following summary shows the degree of fallacy resulting from the use of the E. and E. method which has to be allowed for :

Year.	Cases in which T.B. were found <i>only</i> by the E. and E. method, which lost their T.B. and are thus recorded in the tables.	Cases positive to ordinary methods, which lost T.B. as shown by the same methods, but were still positive to the E. and E. examina- tion, and are record- ed as not having lost T.B.
1910-11	.	2
1911-12	.	8
1912-13	.	1

The records for the year 1910-11 are unaffected, the two cases in the left-hand column being balanced by the two in the right-hand column.

In the year 1911-12 8 cases which are recorded as having lost their bacilli have to be eliminated, and in the year 1912-13 one case.

Thus amended, the figures for loss of bacilli for these last two years are as follows :

	Group.	No. of Cases.	Lost T.B.	Percentage.
1911-12 {	I . . .	34	13	38.2
	II . . .	112	20	16.9
	III . . .	46	2	4.3
All cases .		192	35	18.2
1912-13 {	I . . .	17	9	52.9
	II . . .	100	23	23.0
	III . . .	43	3	6.9
	All cases .		35	21.8

and the records for successive years from 1908 onwards :

1908-09	.	.	16.7%	1911-12	.	.	18.2%
1909-10	.	.	14.5%	1912-13	.	.	21.8%
1910-11	.	.	14.5%				

Thus, after the elimination of the E. and E. fallacy, there still remains to be accounted for a slight advantage in the figures for 1911-12 and 1912-13. Can this advantage be attributed to tuberculin ? During the year 1911-12, although only 32 patients were treated with tuberculin, no less than 13 or 40% of them lost their T.B. Is this sufficient to account for the improvement in the net results ? I can find no other factor to be considered, since in respect to length of stay the average period of residence in the sanatorium during the year in question was somewhat shorter than in any previous year.¹ During the year 1912-13, however, the length of treatment of the patients was distinctly longer than formerly, some five weeks on the average. This no doubt accounts for a good deal of the improvement in the results for these twelve months, but how much it is impossible for me to estimate.

It is doubtless possible for an actuary to answer these various questions. For example, if supplied with the necessary data he should be able to determine the loss of T.B. in each group for varying periods of treatment in the sanatorium (a) in the pre-tuberculin days, and (b) in the tuberculin era. Information on these heads will allow of his estimating to what extent, if any, the use of tuberculin on the one hand, and increased length of treatment on the other, has favourably affected the results for the years 1911-12 and 1912-13.

¹ Prof. Pearson suggests that possibly the cases generally in this year were of a more favourable type than usual. I have also been unable to allow for the fact that four patients lost T.B. before they began treatment by tuberculin.

For the present, it seems best to place these facts before the reader of this report, and to allow him to draw his own conclusions from them. For a critical analysis of the statistics, he is referred to Prof. Karl Pearson's prefatory note. As Prof. Pearson points out, the statistics are of little value, indeed, may be positively misleading, until various sources of fallacy have been eliminated. It has, however, been decided to publish the figures as they stand, in the belief that by so doing the extreme care necessary in order to attain to the highest possible standard of accuracy may be made clear to other workers in the same field.

SECTION XIX

Observations on the Suggested Use of Tuberculin in Dispensaries and in general practice throughout the Country

IT has been strongly urged that our best hope of dealing satisfactorily with the problem of tuberculosis lies in the general use of tuberculin. Bandelier and Roepke lay great stress on this point. These physicians, however, whilst "holding it their duty to help their colleagues in private practice, that they may learn to employ the specific treatment of tuberculosis,"¹ recognise the difficulties and abuses which may be associated with the general use of tuberculin.

In my capacity of examiner of candidates for admission to the sanatorium, I have learnt that tuberculin treatment is much more widely practised than was the case some eighteen months ago, and the wish, therefore, that it should be more largely used has, in a considerable measure, been realised. At the same time, I have seen enough to make me doubt whether this increased use of tuberculin is on the whole in the interest of the *average* patient. That it is desirable for the medical practitioner to make himself familiar with the details of tuberculin administration is obvious. It is all the more unfortunate, then, that nearly all writers on this subject, by emphasising the results of treatment of the favourable cases, and ignoring the results of its use in those of a less favourable nature, give the impression that tuberculin treatment is a simpler, safer, and more efficient method than it really is. Suffi-

¹ *Loc. cit.* pp. 281, 287.

cient stress has not been laid on the fact that it is the duty of the practitioner to avoid provoking reactions. A physician who has had wide experience with tuberculin may legitimately take some risks, for he has learned how, by the careful selection of cases, to limit them; but it is a grave mistake to lead the profession generally to think that there is little or no harm attaching to febrile disturbances. It cannot be too strongly insisted that safety lies in the avoidance of reactions. There is abundant evidence to show that at the present time this most important fact is not realised.

SECTION XX

Records of Cases treated with Tuberculin in private practice and at Dispensaries and elsewhere

THE following are brief reports of some cases which have come under my immediate notice during the past twelve months. Chart 18, which refers to them, will be found on page 103.

All these patients applied for admission to King Edward VII Sanatorium :

CASE 25

Mr. X, a schoolmaster, gave the following history:

Pulmonary Tuberculosis was first recognised in 1911. He was treated in a sanatorium until the spring of 1912; as a result he was much benefited, and returned to work. In June 1912 he began a course of tuberculin at a London dispensary. At this date, the chest and larynx were examined, the latter being pronounced normal. No subsequent examinations were made at any time. The first course of tuberculin commenced on June 4th and finished on September 6th with a dose of 1 c.c. This course was practically reactionless throughout, two inoculations being given weekly. The patient felt well, gained some weight, and continued his ordinary occupation. On September 10th he began a second course of tuberculin (bovine tuberculin was given in both courses) and at once developed signs of intolerance. At every increase of dose he had a reaction, but usually after three repetitions of the dose it could be fairly well tolerated. As the tuberculin became stronger, the reactions became more intense. On eighteen occasions the temperature rose to from 100° to 101.5°, and with the fever were associated severe pains in the limbs, back, and abdomen. Often, too, there was severe

vomiting, coming on within a few hours of the inoculations and lasting for about twenty-four hours. Usually these violent reactions subsided in from twenty-four to thirty hours, leaving the patient in a state of exhaustion. These disturbances were apparently not regarded as anything at all unusual, and for four months (up till the end of January 1913) tuberculin treatment was persisted with in spite of them. Throughout the whole of this time the patient suffered from continued malaise, which, although never absent, was aggravated by each inoculation. Very soon he became unfit for work: to quote the patient's own words, "When not in bed with fever I was too exhausted to do anything." The weight steadily dropped from 9 st. 7 lb. to 8 st. 12 lb., and cough increased. Finally, at the end of four months of continued ill health, he broke down with a severe attack of tachycardia.

At the dispensary he was not examined, but was told that he had developed a mixed infection, and that for the time further tuberculin treatment was not indicated.

This patient applied for admission on April 29th, 1913, and was admitted to the sanatorium on May 19th. On examination at this date his condition was as follows:

There were signs of extensive disease in the upper and lower lobes of both lungs, and there was also tuberculosis of the larynx. The general condition was unfavourable. He was quite unfit for work, and likely to be so for many months. He was 9 lb. below his normal weight. The temperature touched 100° F. every evening, and the pulse-rate varied from 96 to 110. The sputum contained T.B. The temperature and the pulse-rate gradually yielded to a course of complete rest.

This patient is still under treatment in the sanatorium.

CASE 26

Mr. Y, a draper, gave the following history:

Pulmonary Tuberculosis was diagnosed in October 1911, but there is no record available as to his condition at this date. He was at once given a course of tuberculin treatment, which lasted in all for fourteen months, the following tuberculins being used: P.T.O., B.E., and A.F. The treatment was marked

94 PRELIMINARY REPORT ON TUBERCULIN

by a good many reactions of moderate severity. During the fourteen months there was a steady loss of weight, amounting to 28 lb. Shortly after completion of the course, he applied for admission to this sanatorium, and was admitted on February 24th. On examination at this date he was found to be suffering from extensive disease of both lobes of the left lung and disease of the upper lobe of the right lung. There was also somewhat extensive tuberculous disease of the larynx. The general condition was unfavourable. He was 26 lb. below his normal weight, was markedly febrile, a temperature of 101° being recorded every evening, and the pulse-rate ranged from 100 to 104 per minute. The sputum contained T.B.

He was treated in the sanatorium for five weeks, but beyond a gain of weight of 6 lb., and a slight degree of improvement in general health, his condition on discharge was unaltered.

CASE 27

Mrs. A.—Pulmonary Tuberculosis was diagnosed in 1912. The onset was acute, and she at once went to a sanatorium. After two weeks' treatment she was afebrile, and convalescence was rapidly established. At the end of six weeks the disease in the lung was reported to be quiescent. On April 14th, when the patient had been afebrile for a month, and was walking several miles daily, tuberculin treatment was begun, two doses of a bovine preparation being given weekly from that date up to May 19th. There were no reactions until May 6th, but from the first inoculation the patient's sputum doubled in amount. On May 8th, the day following the inoculation, there was a rise of temperature to 104·2°, and a normal temperature was not regained for five days. A few days later another inoculation was given, which was followed by a slight reaction. Four days later, another inoculation was given, which was followed by a steady rise of temperature to 101° F. This was the beginning of a febrile disturbance lasting for six weeks, and since then the degree of convalescence which existed before tuberculin was given has not been re-established.

This patient was admitted to this sanatorium on February 25th, on a month's probation.

Her condition then was as follows:

There were signs of active disease throughout the right lung and in the upper parts of both lobes of the left lung; and there was tuberculous ulceration of both vocal chords. Her general condition, although her weight was normal, was unfavourable. She was definitely febrile, her evening temperature rising to about 100° F., and she had about 6 oz. of sputum daily, containing T.B.

She remained at the sanatorium for fourteen weeks, but failed to make any appreciable improvement, and died three months later.

CASE 28

Mrs. L.—Pulmonary Tuberculosis was diagnosed in August 1909, and after five months' treatment recovery was believed to be complete. She continued in good health until the latter end of 1911, when symptoms of disease in the lung again developed, and in January 1912 she began a course of tuberculin at a dispensary. The following are copies of the records made by the medical officer of the dispensary during the treatment of this case:

	Dose. c.c.		
March 22. P.T.O.	.001	.	In bed afterwards
	.0014	.	,
	.002	.	Temperature 102° (Bed)
	.0018	.	,
	.0014	.	,
	.002	.	,
	.0014	.	,
	.0018	.	,
	.0022	.	,
	.002	.	,
	.002	.	,
	.002	.	,
	.0024	.	,
	.0028	.	,
	.003	.	,

Five days later (May 30th) the temperature rose to 103.2°. Interval of eight days.

·0002	·	·	·	·	·	Temperature 99.4°
·0004	·	·	·	·	·	99.8°

Five days later (June 15th) the temperature rose to 101.8°. Her last inoculation was given on July 15th.

She was admitted to this sanatorium on July 18th, 1912. When examined at that date the patient had signs of active disease in the upper and lower lobes of the right lung, and tuberculous disease of the larynx. Her general condition was unfavourable. She was 7 lb. below her normal weight, and had slight fever. Her sputum averaged 1 oz. daily, and contained T.B. She was treated in the sanatorium for thirteen weeks, but beyond a gain of 11 lb. she made no appreciable improvement.

CASE 29

Miss T.—Pulmonary Tuberculosis was diagnosed in August 1911, and in October she commenced a course of tuberculin treatment, which terminated eighteen months later, in April 1913. *This course of treatment was conducted entirely through the post.* The patient herself administered the inoculations which were sent to her, and she in turn sent away a record of her four-hourly temperature chart ; these charts were usually sent off twice a week on the evening of the second day after the inoculation. She was not under the care of any local practitioner, and her chest was only examined on three occasions during these eighteen months of treatment. For the first five months she did well, gaining weight and losing her cough. Almost from the first she had a certain number of reactions, with malaise, but the temperature thus raised rarely remained up for more than forty-eight hours. During the summer of 1912, in spite of a constantly raised temperature (her temperature now did not drop to normal during the intervals of the inoculations), her cough diminished. In November 1912 she started another variety of tuberculin. This at once gave rise to increased malaise, and following the inoculations the

PRELIMINARY REPORT ON TUBERCULIN 97

temperature rose regularly to from 100° to 101°, and not infrequently to from 101° to 102°. At this date one inoculation was given a week, and throughout the interval the temperature ranged from 99° a.m. to a little over 100° p.m. With the increase of fever following each inoculation, there was back-ache, stiffness and pains in the joints, headache and vomiting, these more acute symptoms lasting for some days. During December she had no further injections, and in this period the temperature dropped to a somewhat lower level. The inoculations were recommenced in January 1913; they were, as before, received through the post, and self-administered. Again there was a frequent repetition of reactions. The cough became incessant, and the patient became very weak, an unpleasant symptom being a feeling of faintness when in bed. Her condition became an anxiety to her family, and tuberculin was discontinued in the middle of February.

She applied for admission to this sanatorium on March 10th, 1913, and was admitted on March 26th. On examination at this date her condition was found to be as follows:

Right lung—disease of the greater part of the upper lobe, with some fibrosis, and of the upper third of the lower lobe. Left lung—disease of the upper third of the upper lobe. The general condition was fairly good; weight normal; slight fever; pulse-rate 85 to 95. There was a good deal of sputum, which contained tubercle bacilli. Treated for two months with complete rest, she made favourable progress, and her temperature fell to a normal range, but the pulse-rate remained between 80 and 90.

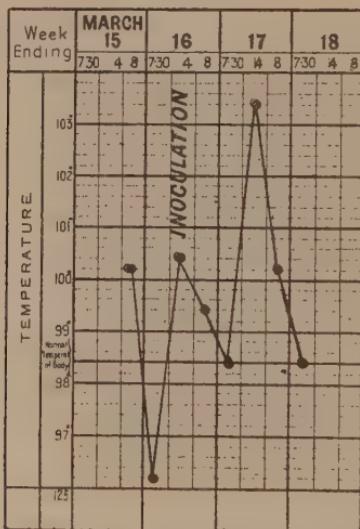
This patient stated that she had lived under exceptionally favourable conditions throughout the tuberculin treatment, had rested continuously, and had made every effort to keep up her weight.

CASE 30

Mrs. W.—A case of chronic disease of some four years' duration, with periods of complete arrest. Tubercle bacilli were found in June 1908, and she was treated in this sanatorium from June 11th, 1908, to September 18th, 1908. She was

discharged with signs of arrested disease, and with no T.B. in her sputum. In the summer of 1911 she felt unwell and had a course of ten tuberculin inoculations, which seemed to benefit her. In the following January she began a second course, which finished in April. This course was not so satisfactory, as she had increased fever throughout. In July of the same year she began a third course, which was terminated nine months later by an attack of "congestion of the lungs." All through this course the tuberculin provoked reactions. At first her temperature rose to 100° only, remaining up for some three days, but there was much malaise. She stated that for the last three months the reactions had been much more severe, temperatures of 102° and 103° being frequently recorded, and on several occasions 104° . She produced some of the charts of this last period, which record reactions up to 103.4° . The following Chart, No. 17, shows a

CHART 17.



typical reaction. The patient felt very ill all through these months of intense reactions, and lost flesh rapidly; unfortunately exact records as to the loss of weight are wanting, as she was not weighed.

She applied for admission to this sanatorium on May 4th.

PRELIMINARY REPORT ON TUBERCULIN 99

and was admitted on May 31st, 1913. On examination at this date, the following was her condition :

Left lung—physical signs suggested almost complete excavation of the whole of the lung ; the breath-sounds throughout were cavernous, with an almost amphoric quality ; there was whispering pectoriloquy and some crepitation on cough towards the base. In the right lung there were signs of active disease in the upper lobe. The general condition was most unfavourable ; she was 31 lb. below her normal weight, the temperature ranged from 99° a.m. to 100·8° p.m., and the pulse was from 80 to 100. The sputum was abundant and contained T.B.

This patient is still in the sanatorium, and has made some substantial improvement.

CASE 31

Mrs. K. History : An attack of influenza in August was followed by cough, and in September Pulmonary Tuberculosis was diagnosed. She was then kept in bed for three months. At the end of a further three months she was much better. Weight had been gained, appetite was good, and temperature for the most part was normal. Convalescence, in short, was in a considerable measure established. At this date (November 1912) she began a course of tuberculin, of which the following brief account was given by the patient's husband :

“ There were eight inoculations, for the most part at ten-day intervals. There was never any noticeable alteration in temperature until the fourth or fifth day after inoculation. It then began to go up and to assume an inverse type, the morning temperature of about 101° being always higher than the evening temperature of about 99°. The period of raised temperature grew longer after each inoculation, so the interval between the doses was lengthened from eight to from fourteen to sixteen days. The treatment was terminated, in March 1913, by the development of pleurisy with effusion. I fear this account is rather scanty, but, so far as it goes, it is dependable. I particularly noticed the behaviour of the temperature, as it was not what our doctor seemed to expect.”

She was admitted to the sanatorium on May 19th, and on examination the following was her condition :

Throughout the right lung there was extensive and active disease. The left lung showed fairly extensive disease of both lobes. The general condition was unfavourable ; there was much emaciation, the patient being 23 lb. below her normal weight ; the temperature ranged from 99° a.m. to 102° p.m., and the pulse-rate from 95 to 110. Sputum contained T.B.

In the sanatorium she failed to make any improvement.

CASE 32

The record of the following case has been kindly given to me by the practitioner :

Mrs. N had an attack of haemoptysis in 1910. Throughout a considerable part of the year 1911 she was in a sanatorium and made a good recovery. In August 1912 she became pregnant, but had a miscarriage in January 1913. This weakened her considerably, and symptoms of Pulmonary Tuberculosis again showed themselves. The temperature at this time was normal, varying from 97·8° a.m. to 99° p.m.

Tuberculin treatment was begun on February 20th, and the following is the record of her reactions.

<i>Feb. 20th, 1st dose</i>	.	No reaction. Temperature normal.
<i>,, 23rd, 2nd dose</i>	.	No reaction. Temperature normal.
<i>,, 25th, 3rd dose</i>	.	Rise of temperature to 100° F., with some malaise.
<i>,, 27th, 4th dose</i>	.	Rise of temperature to 101·6°, with headache and coloured sputum. The fever persisted for four days, the temperature being normal again on March 5th.
<i>Mar. 6th, 5th dose</i>	.	Rise of temperature to 102°, falling to normal on the 8th.
<i>,, 12th, 6th dose</i>	.	Rise of temperature to 100°, normal again on 14th.

PRELIMINARY REPORT ON TUBERCULIN 101

Mar. 18th, 7th dose . Rise of temperature to 103·4°; the state of fever lasting until the 24th.
,, 27th, 8th dose . Rise of temperature to 101°, falling to normal on the 29th.
April 3rd, 9th dose . Rise of temperature to 99·8°, falling to normal on the 6th.
,, 11th, 10th dose . Rise of temperature to 104°, the febrile condition lasting for seven days.

Throughout the tuberculin treatment the patient suffered from malaise, and towards the end also from haemoptysis, general weakness, and faintness. After the tenth inoculation, tuberculin was discontinued on account of cardiac weakness and continued faintness.

In May she applied for admission to the Midhurst sanatorium, and was admitted on June 14th. Her condition then was as follows :

Pulmonary lesion. The physical signs suggested arrested disease of both lobes of the left lung. General condition poor. Weight, 14 lb. below her average normal. Marked fever, the temperature ranging from 100° a.m. to 101·8° p.m. The pulse, which was weak, varied from 85 to 100 per minute. There was practically no sputum.

This patient has only been in the sanatorium for a short time. She is still febrile, but the temperature is steadily falling.

CASE 33

Mrs. R gave the following history :

Cough began in the spring of 1912. Pulmonary Tuberculosis was first definitely diagnosed early in February 1913, at which date T.B. were found in the sputum. On February 5th, the patient consulted Sir R. Douglas Powell, who recommended sanatorium treatment, and to him I am indebted for the following description of her condition at that date :

“Mrs. R. looks pale and worn and her pulse is quick.

102 PRELIMINARY REPORT ON TUBERCULIN

There is a small group of enlarged glands in the left upper neck. The physical signs are limited to the upper third of the left lung. The resonance is impaired over the left clavicle, subclavian and upper scapular regions, and there are coarse crackling râles indicative of caseous foci undergoing softening, the signs being especially well marked over the posterior part of the region affected. A week ago some evening rise of temperature was noted, but is now said to be normal."

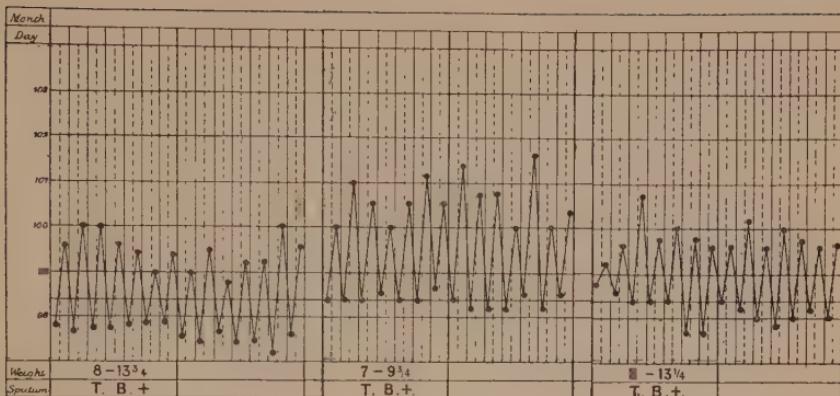
A few days subsequent to the consultation with Sir Douglas Powell, the patient began a course of tuberculin, the inoculations being given at intervals of eight days. The first five inoculations were well tolerated: there was no reaction, the evening temperature usually being no higher than 99° F. The patient was feeling well, was up and about all day, and was obviously improving in health. After the sixth inoculation the temperature rose somewhat, and after each subsequent inoculation it rose higher and remained at the higher level throughout the intervals of inoculations. The patient says that the highest temperature recorded was 102°, and on the day of its occurrence her doctor feared the development of inflammation of the lungs. For the last four weeks of tuberculin treatment, the temperatures ranged between 99° a.m. and 101° p.m. She felt very ill and tired, lost weight, cough increased, and the sputum doubled in amount.

She was admitted to the sanatorium on April 24th, two weeks after receiving the last inoculation. Her condition then was as follows:

There were signs of active disease throughout the greater part of the upper and lower lobes of both lungs. The general condition was markedly unfavourable. She was 12 lb. below her normal weight, and the temperature ranged from 98·4° a.m. to from 100° to 102° p.m. The amount of sputum averaged several ounces daily, and T.B. were present.

The accompanying chart shows the temperature on admission of the nine cases just recorded.

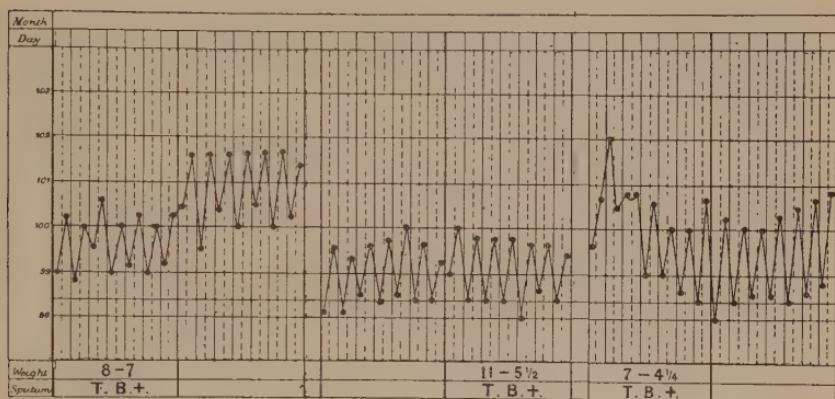
CHART 18.



Case 25.

Case 26.

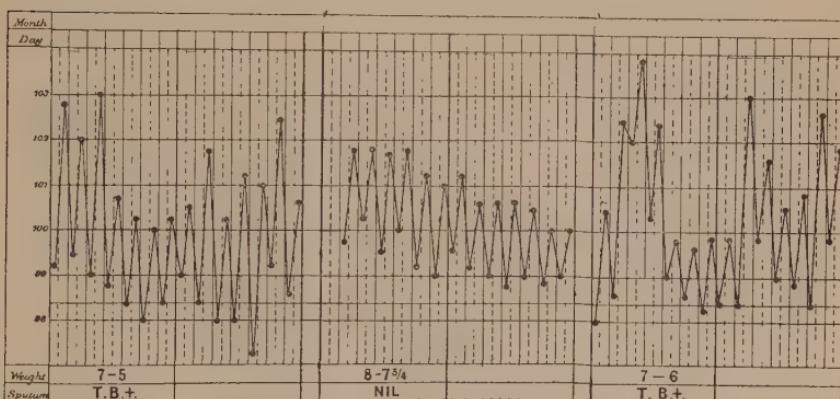
Case 27.



Case 28.

Case 29.

Case 30.



Case 31.

Case 32.

Case 33.

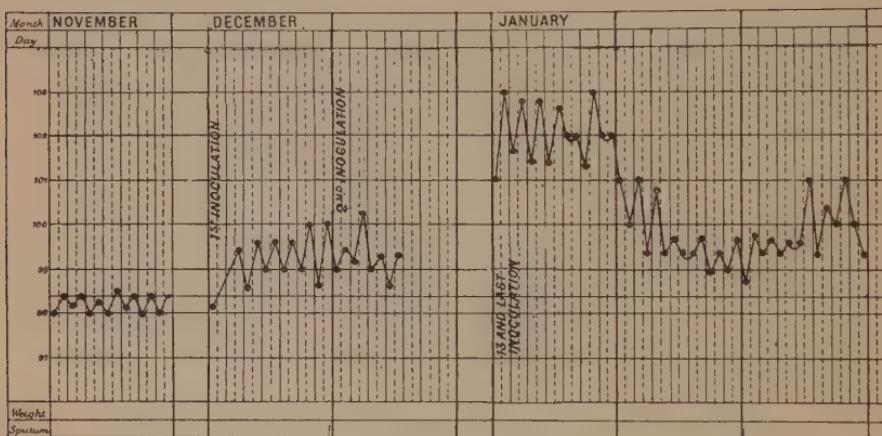
CASE 34

Miss B gave the following history:

In July she had a slight cough. At the first examination of her sputum, tubercle bacilli were found on one slide only, and all subsequent examinations were negative.

When admitted to this sanatorium, on August 27th, 1912, the physical signs were limited to some impairment of resonance at the apex of the right lung, with an occasional inconstant adventitious sound after coughing. The temperature was

CASE 34. CHART 19.



Before Tuberculin Treatment.

During Tuberculin Treatment.

After Tuberculin Treatment.

normal, the weight 4 lb. above her average normal weight, and the physique and general condition of the patient were good. There was no sputum.

Progress in the sanatorium was uneventful. After a few weeks nothing remained in the way of physical signs except the slight impairment of resonance at the right apex. She was discharged on November 26th, 1912, with signs of arrested disease, in excellent general health, 10 lb. above her average weight, and walking six miles daily.

A few weeks later she began a course of tuberculin treatment.

under the advice of a practitioner. From the first inoculation the temperature rose, and very soon became definitely febrile. With the fever were associated constant malaise, shivering, nausea, and not infrequently vomiting. There were no cough, sputum, or body pains, but the patient felt ill. After the thirteenth inoculation the temperature for a week ranged between 101° a.m. and 103° p.m. Tuberculin was then discontinued, but for ten weeks the patient was confined to bed. When the fever and acute symptoms had subsided she went to the seaside and lived a quiet open-air life. She rapidly recovered, and when examined, five months after her last inoculation, she was in excellent health, with the exception of some enlarged glands in the left axilla which had developed during the febrile attack. The lung disease was still arrested.

On the accompanying chart (Chart No. 19) the temperature of this patient is shown (a) before the tuberculin treatment was begun, (b) during the period covered by the first two inoculations, and (c) on the day of the last inoculation, and for three weeks subsequently.

CASE 35

Mr. R. D. Age 32.

Admitted to the sanatorium in October 1913; gave the following history:

Pulmonary Tuberculosis was diagnosed in January 1911, the disease at that date being limited to the apices of both lungs. Up till the end of September of the same year, he was treated with inhalations and followed his ordinary occupation. He appeared to make little or no progress, and in October consulted a specialist, who told him that he had consumption in the second stage in both lungs, and recommended tuberculin. The larynx was not examined.

The first course of tuberculin began in October 1911, and ended at the latter end of May 1912. This treatment was directed by correspondence, the doses of tuberculin being posted to the patient twice a week, and the patient inoculating himself in the thigh. He received the following written instructions: "If the temperature is 99.5°, wait a day. If

the temperature is 100° F., wait two days. If the temperature is 100·5°, wait three days. If the temperature is more, wait for another dose."

The patient understood by these directions that the usual interval of three days between the doses should be increased by one day, two days, or three days, according to the height of the temperature. During the first eight months of the treatment, the patient had very few reactions, the temperature not rising above 100° F. on any occasion. The weight remained constant, the sputum did not alter in amount, and, in general, the clinical condition appeared to be unaltered. In March 1912, however, the patient complained of hoarseness; he consulted his physician, who diagnosed acute laryngitis, and recommended as much rest of the voice as possible. This occasion was the first on which the patient had seen a medical practitioner since the tuberculin treatment was begun in the previous October.

From the latter end of May to the latter end of June 1912, tuberculin was discontinued owing to the specialist being away on a holiday. In June the larynx was again examined and tubercular ulceration diagnosed. The patient was then advised to give up his business for at least a month, and to go to the seaside and rest his voice. His chest was not examined. This month's holiday, during which no tuberculin was given, had a beneficial effect, the patient gaining weight and improving in general health. On his return home in July his larynx was again examined and pronounced to be much better.

Throughout August, September, and October the patient followed his usual occupation. During this period he did not consult any medical practitioner and followed no treatment, his condition, as far as he could judge, remaining unaltered. In November he again consulted the specialist, and on his advice began a second course of tuberculin, which ended at the end of January 1913. This course was also directed by means of the post, the patient meanwhile following his ordinary business. Throughout November and the first three weeks of December the tuberculin did not give rise to any reactions, but during the latter part of December marked

reactions constantly occurred, the temperature frequently rising to 102 on the day following the inoculations. In spite of these reactions, the patient managed to follow his business, except on a few days when the temperature was unusually raised. The body-weight remained constant, and there was no appreciable increase in the amount of sputum. At the end of January he again consulted his physician, who reported, after examining the larynx, that further tuberculin treatment was at the time undesirable, and recommended a month's interval. The chest was not examined. At the end of this interval of four weeks, during which the patient had markedly improved in general health and had gained 5 lb. in weight, he wrote for further instructions, and was advised to wait another three or four weeks before making a fresh start with tuberculin. During this period the patient thinks he lost ground, since his general health deteriorated and his cough increased. At the end of the four weeks, realising that he was getting worse, he again consulted his physician, who, after examining his larynx, instructed him to keep a careful record of his temperature for the three following days, to send it by post, and to await instructions. The temperature was found to be 100° F. or more of an evening, and the patient received a reply to the effect that he was not fit to be at work, and should rest for at least a week. In spite of resting, however, the temperature rose to 102° on most evenings. At this point the patient consulted a local practitioner, and after three weeks' rest in bed the temperature fell to normal. The temperature records during these three weeks were sent up to the specialist, who replied that "Now that the temperature is steady, you could have further treatment, and I should advise it." The patient, however, decided to give up tuberculin, and acting on other advice he entered a sanatorium in May.

I am indebted to the medical superintendent of the institution for the following report of the patient's condition in June: "He had then been four weeks in the sanatorium; he had been gaining weight, his condition was fairly good, and his temperature was normal. In the right lung there were signs of disease in all three lobes, and in the left lung signs of ad-

vanced fibrocaseous disease involving the upper lobe and the upper half of the lower lobe. The voice was very hoarse, and in the larynx there was disease on the left side, involving chiefly the arytenoid and the aryteno-epiglottic fold. There was a good deal of local swelling, some ulceration, and general hyperæmia of the larynx."

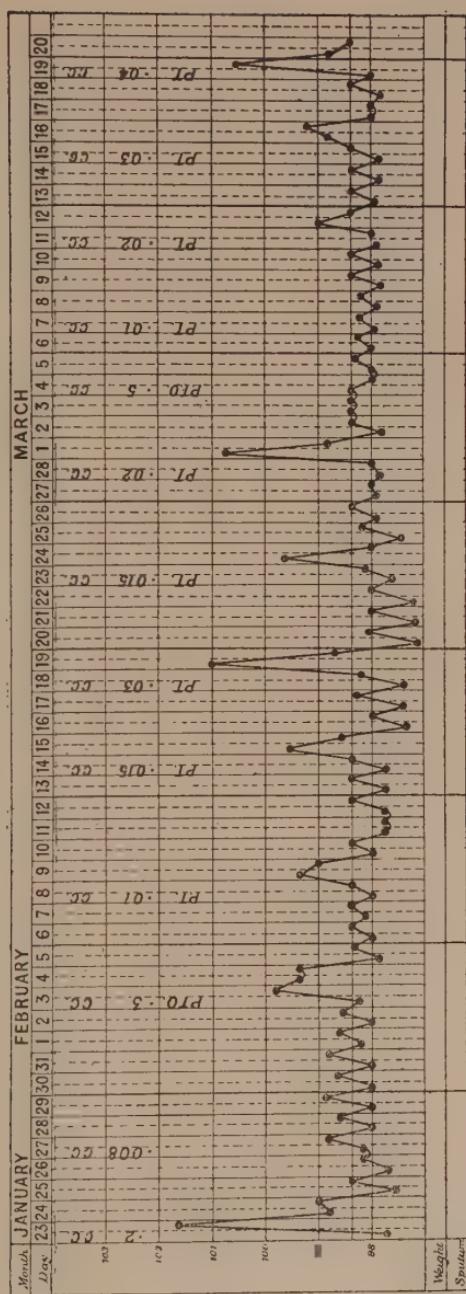
He was admitted to the King Edward VII Sanatorium in October 1913. At that date there were signs of chronic disease in all the lobes of both lungs, with evidence of a considerable amount of fibrosis. In the larynx there was indolent thickening in the left ary-epiglottidean fold and in the anterior end of the right vocal chord. The temperature-range and the body-weight were normal. The daily amount of sputum averaged some 3 iv, and T.B. were present.

CASE 36. CHART 20

Mrs. A, age 30, who applied for admission to the sanatorium in October 1913, sent with her application the following account of her illness:

Pulmonary Tuberculosis was diagnosed in March 1912, tubercle bacilli being found in her sputum. In July 1912 she saw a specialist, who found evidence of slight disease limited to the upper lobe of the right lung, the disease in his opinion already being very considerably arrested. He advised the patient to live at home on sanatorium principles, the case being too slight a one to require residence in a sanatorium. Further, the case being such an exceptionally favourable one, he recommended the use of tuberculin. In the following month (August) tuberculin treatment was begun, but after the first three or four injections blood appeared in the sputum. This appearance of blood was believed to be unconnected with the use of tuberculin, but the specialist advised that it would be safer to discontinue the inoculations. In September, laryngeal symptoms developed, and a laryngologist was consulted, who recommended vocal rest and further tuberculin treatment. This advice was followed. In the course of December there occurred a second period of blood-stained sputum, associated with higher temperatures. Tuberculin was then discontinued, and after a few weeks in bed the sputum became clear

CASE 36. CHART 20.



again and the temperature fell to normal. Tuberculin inoculations were then recommenced. Reactions now became more frequent, the voice became more and more husky, and in January 1913 went altogether, the throat becoming swollen and uncomfortable. However, tuberculin treatment was still persevered with. In June 1913 the patient was taken ill after having an inoculation, and went to the seaside for a change. She remained in bed at this time, but in spite of the rest the temperature remained febrile. The inoculations were still being given. At the end of July tuberculin treatment was abandoned. On October 22nd the patient consulted Sir St. Clair Thomson, whose report on the condition of the larynx at this date is as follows :

"There is infiltration and ulceration on the left edge of the epiglottis, considerable chronic infiltration of both arytenoids, ulceration on the edges of the overhanging ventricular bands, and fixation of both vocal chords in the cadaveric position."

A few days later she had an attack of acute pleurisy on the left side, her temperature rising to 101.8°.

This patient has also sent to me her temperature charts during the period covered by her tuberculin treatment ; and from these charts I have copied the accompanying record (Chart 20) for eight consecutive weeks.

The following additional notes made by the patient are of interest :

The tuberculin injections were given in the evening, and the temperature was frequently higher in the night than is recorded in the charts, the higher temperatures frequently being accompanied with vomiting. I had difficulty in persuading my doctor to keep the doses as low as he did, his aim being a complete course in three months, and throughout the treatment I allowed longer intervals between the doses than he recommended. The reactions started a discharge from the right ear, but this has ceased under treatment and since the tuberculin was left off.

This patient proposes to enter the sanatorium when she has recovered from her present acute illness. I am unable, therefore, at present to give a report as to the condition of her lungs.

CASE 37. CHART 21

Mrs. K, age 41, gave the following history :

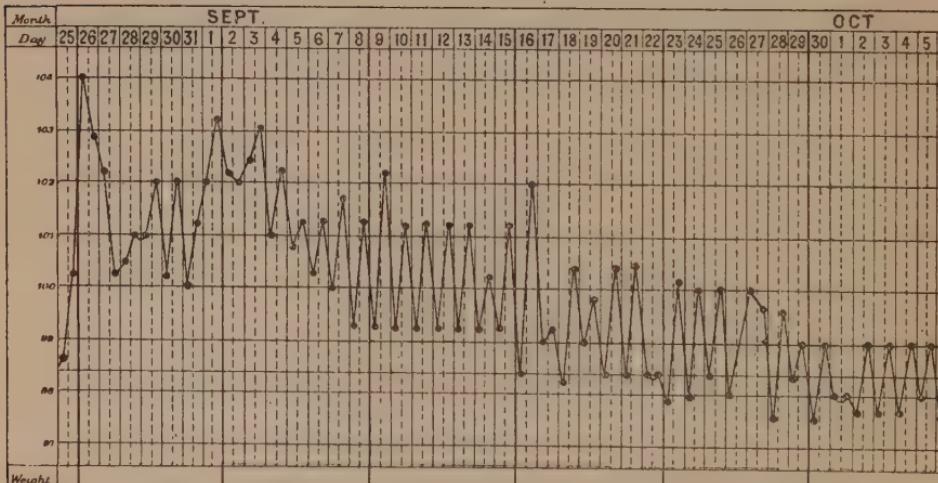
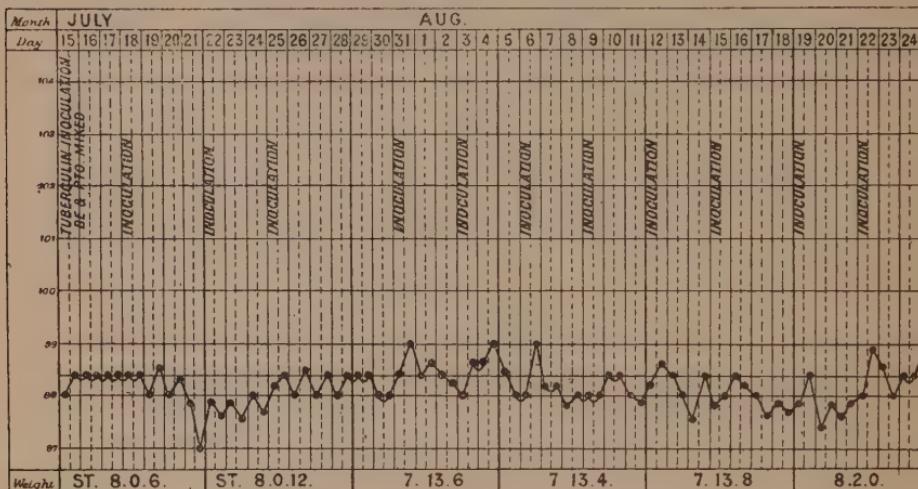
Cough began in February 1912, but there was no sputum. In May 1913 she had some sputum for the first time, and on examination it was found to contain tubercle bacilli. In the following month she began a course of tuberculin, the inoculations, which consisted of a mixture of P.T.O. and B.E., being given twice a week. At this time she again had no sputum. The first twenty inoculations did not give rise to any symptoms except for some slight malaise, the temperature throughout remained at a normal level, and the patient's progress in every way was satisfactory. On August 20th she complained of severe pain in the right side, which was relieved somewhat by having the side strapped. On August 22nd she received her last inoculation ; on the 23rd and 24th she felt very unwell, but there was no appreciable rise of the temperature. On the 25th it rose suddenly to 104° F., the rise occurring quite suddenly and being accompanied with pain of a most intense character in the right side, which was only partially relieved by morphia. This ushered in an acute febrile illness, which lasted for six weeks and was marked by signs of pneumothorax, consolidation, and pleurisy in the lower lobe of the right lung. The accompanying chart (No. 21) records the patient's temperature during this illness.

On her admission to the sanatorium in November, the physical signs suggested extensive chronic disease of long standing, chiefly affecting the right lung. In the left lung there were signs of infiltration at the apex. On the right side there was considerable loss of movement throughout, with signs of retraction and marked loss of resonance from apex to base. In the upper lobe the breath-sounds were weak and bronchial in type, becoming cavernous towards the axilla, with whispering pectoriloquy and fairly numerous crepitations. Over the lower lobe there was bronchial breathing with numerous crepitations to the inferior angle of the scapula, and below this point to the base the breath-sounds were of a cavernous character, with pectoriloquy and some crepitations on cough. Her general condition was very fair, and she was

112 PRELIMINARY REPORT ON TUBERCULIN

up to her normal weight. There was a slight degree of fever, which was lost after a few days' rest. There was no sputum.

CASE 37. CHART 21.



It is possible that the acute illness was not associated with the tuberculin inoculations, but this is not the opinion of

PRELIMINARY REPORT ON TUBERCULIN 113

the medical practitioner who was in charge of the case. The clinical history is strongly suggestive of the cumulative action of B.E., which is familiar to all who have worked with this preparation.

CASE 38

Mr. W, age 37—admitted to the sanatorium in October 1913—gave the following history:

Cough began in 1904, and in January 1905 tubercle bacilli were found in the sputum. The patient, who was living in America at the time, then came home to England, and was treated in a sanatorium for twelve weeks (without tuberculin). He derived great benefit and returned to America apparently in good health. There was no disease in his larynx at this time. During the next three years he maintained his health, but never quite lost his cough. In December 1908 he developed tuberculosis of the larynx. He then went up to the Argentine mountains and strictly carried out sanatorium life. Eight months later, a laryngologist pronounced the larynx cured, but found signs of active disease in the lungs. He remained in the mountains until the spring of 1911, when, his health again failing somewhat, he returned home for another course of sanatorium treatment. He entered a sanatorium in July. At this date both lungs were affected, but the larynx was pronounced to be sound. His general condition was unfavourable; he was 14 lb. below his normal weight, and had some fever of an irregular type. He remained in the sanatorium for eleven months, and throughout the whole of this period was treated with tuberculin, four complete courses being given, of P.T.O., P.T., O.T., and B.E. respectively.

On P.T.O. he had comparatively few reactions, but on P.T. the reactions were frequent, the temperature often rising to 103°. He was usually in bed for two days after each inoculation and felt fairly well on the third day, when another inoculation became due. He thus suffered almost continuously from malaise, and could take but very little exercise.

On O.T. the reactions were again less marked, but on B.E. he reacted more actively. On his discharge in May 1912, his condition was unchanged except for a gain of 9 lb. in weight. He was still febrile, and his sputum, which was unchanged in amount, contained bacilli. After leaving off tuberculin, his general condition improved, and three months later (October 1912) he returned to America. Two months later hoarseness developed, and early in this year he returned to England. On his admission to the sanatorium in August, his condition was as follows: There were signs of extensive chronic disease throughout both lungs, and in the larynx there was indolent infiltration of all the laryngeal structures, with partial loss of the epiglottis and ulceration of both vocal chords.

FURTHER RECORDS OF CASES TREATED WITH TUBERCULIN IN PRIVATE PRACTICE AND AT DISPENSARIES AND ELSEWHERE

In the course of preparing the annual report of the sanatorium for the past year, I have obtained further data as to the use of tuberculin in this country. It is our practice at the end of each year to send to every patient who has been discharged from the sanatorium, since the institution was opened, a printed form asking for information with regard to the present state of health, the treatment, if any, at present followed, etc. This annual census for the year 1913 has just been completed, and replies have been received from patients who are living in various parts of the United Kingdom. Of this number fifteen stated in their returns that they had been receiving tuberculin treatment. The small number of patients who have undergone tuberculin treatment since leaving the sanatorium suggests that tuberculin has as yet made but small appeal to those who have been educated in sanatorium principles.

The following are the reports, amplified in most cases by notes from medical practitioners, sent in by these former patients who have had tuberculin. They are recorded just as they were received, whether favourable or unfavourable in character, complete or incomplete, so that there should be no question of any selection having been made.

CASE 39

Miss D. Age 32.

Type of case, moderately advanced disease (Group 2).

Discharged from the sanatorium November 1911.

Result.—No improvement. Condition unfavourable. Temperature 98.4° to 99.4°. Weight 9 lb. below normal. T.B. present.

In her report, dated September 1913, the patient states:

“ My present health is very good. I am still carrying out the open-air treatment, with rest. Immediately after leaving the sanatorium, I underwent tuberculin treatment, and continued it for a year, with most satisfactory results.”

The patient's medical attendant has been good enough to send me the following details:

“ She commenced her course in December 1911, and finished it in March 1913. Last week I gave her some test injections of O.T. up to 1 c.c. without producing any reaction, from which I conclude that she is well immunised. She has extensive fibrosis of her right lung, and of the apex of the lower lobe of the same lung, but is quite free from crepitations. She is apparently in perfect health, and bacilli disappeared from her sputum after six months' treatment. At present she has no sputum. She has not varied a pound in weight throughout the treatment. She tells me she can walk seven or eight miles without distress.

“ In respect to dosage: In practically all my cases I give .0005 P.T.O. up to 1 c.c.; then I change over to .002 P.T., increasing to a full c.c., then 1 c.c. of O.T., increasing to a full c.c. I gave the P.T.O. at intervals of four days, the P.T.

at five days, and the O.T. at six or seven day intervals. I aim at mild reactions, but however carefully one increases doses, occasionally one gets more reaction than is desirable. Miss D seldom exceeded 100° F."

CASE 40

Mr. B. P. Age 29.

Type of case, advanced chronic disease.

Discharged from the sanatorium in November 1911.

General condition unfavourable. Temperature 98.4° to 99.6°. 7 lb. below normal weight. T.B. in the sputum.

In his "after-history" report the patient writes :

"After leaving Midhurst, I got worse for the next four months, and then gradually began to get better, and have continued to do so. This I believe is due to the tuberculin treatment which I then began, commencing with very weak doses, gradually increasing in strength, but never sufficient to produce a reaction. I continued to follow the open-air treatment, regular exercise, plenty of food, etc. I am now doing light work."

I am indebted to this patient's medical attendant for the following additional information :

"He began tuberculin in February 1912. The dose has been gradually increased from 1/100,000th milligramme. He had no reactions till he reached 1/75 m. He now has 1/100 m. a week without reaction. Previous to February he was taking tuberculin by the mouth, without result. He was at that time apparently going down hill rapidly. Improvement has been gradual and striking. He is now very fairly well. His temperature does not go above 99°. He eats and sleeps well, has no sweats, has put on weight, and enjoys life. In February he was in the depth of despair, very hoarse and very ill. Hygienic conditions, etc., have been the same throughout. *But* the case is by no means cured. There are signs of a cavity at the right apex and râles at the right base. This condition has not altered much during the last few months, except that the signs woke up considerably during the one reaction he had. There is no sputum, and if there were I

should be afraid to test it, as he is easily discouraged. The tuberculin used is New tuberculin."

CASE 41

Mr. G. T. Age 33.

Type of case, early disease (Group 1).

Discharged from the sanatorium January 1910.

Disease arrested. Loss of resonance only at the apex of the left lung. Health completely restored. Exercise: digging in the morning and walking six miles in the afternoon. No T.B. in the sputum. (They were present on admission.)

"After-history" returns for 1911 and 1912, "Well and at work."

In his report for 1913, the patient says: "Health fairly good, but I had a slight haemorrhage a week ago. I am following my usual work, but am living a careful life. I had tuberculin treatment from October 1911 to July 1912."

The following notes have been kindly sent to me by the physician who gave the tuberculin: "Treatment began in October with .0001 c.c. P.T.O. I worked through P.T.O. to .5 c.c., and through P.T. up to .15 c.c., with intervals of three to four days. The last dose was in July, .8 c.c. T.A."

The patient thus describes his impressions of the treatment:

"I had the injections of an evening. This usually meant a somewhat restless night, with little sleep, and a rise of temperature to 100° F. or somewhat higher. The day following, I had a peculiar numbed sort of lassitude and tiredness in the limbs, so that it required an effort to do my work. When I began the treatment I had no actual signs of active disease—for instance, neither cough nor sputum—so I cannot describe the effect of tuberculin upon either. As a matter of fact, I was being attended for another ailment when tuberculin was recommended. Whilst away in the country for a time, during the tuberculin treatment, I regained my normal weight, putting on 19 lb. However, I have since lost 12 lb. of this, and at the present time have both, cough and sputum. I have never felt so well as I did for the eighteen months after leaving Midhurst. I shall not have any more tuberculin, as I have no faith in it."

118 PRELIMINARY REPORT ON TUBERCULIN

CASE 42

Miss L. Age 48.

Type of case, advanced disease of long standing, but with considerable fibrosis (Group 3).

Discharged from the sanatorium December 1908. "Much improved."

The "after-history" reports are as under:

1909. "Doing very well."

1910. "Health not very satisfactory."

1911. "Am wonderfully better."

1912. "Health very fair."

1913. "Not so well as last year, more cough and sputum. Temperature is above normal, and I am easily tired.

"Up to the end of 1912 I enjoyed good health, and had neither cough nor sputum. I had been having tuberculin treatment since the previous spring. However, at the beginning of the year 1913 I had a complete breakdown, and was in bed for four months."

In a letter accompanying the "after-history" return, the patient adds, "I have not proved to be a successful patient in regard to the tuberculin treatment. My doctor was most careful, and I never attained to injections of great strength; none the less, the result has been most disappointing. For the first nine months I was wonderfully well, no cough nor sputum, and I was walking from four to five miles a day. The disease indeed seemed to be arrested. But after the last injection, in December, I completely broke down; every bad symptom returned, and I was in bed for five months. Since this breakdown I have never regained my normal state of health. At any rate, my sanatorium education has been of immense value, having taught me how to live."

CASE 43

Mr. H. Age 47.

Type of case, moderately advanced disease (Group 2).

Discharged from the sanatorium May 1909.

"Much improved." Disease considerably arrested, general health good. Temperature normal. Walking nine miles daily. T.B. still in the sputum.

The "after-history" returns for 1910-12 were all satisfactory. Good health maintained, but T.B. still present in the sputum.

In his report for 1913 the patient stated that he was still feeling quite fit, and had been having tuberculin.

His medical attendant reported as follows: "I gave tuberculin from May 16th to July 2nd, twelve injections of B.E., from 1/50,000th to 1/2,000th. In September I gave six injections, from 1/2,000th to 1/1,000th. There have been no reactions. In my hands, tuberculin has had no effect, good or bad, and I am rapidly losing what little faith I ever had in it."

CASE 44

Mr. C. Age 21.

Type of case, moderately advanced disease (Group 2).

Discharged from the sanatorium May 1912 with disease still active, and with an unfavourable prognosis. After leaving the sanatorium he continued the open-air treatment in the country with beneficial results, the disease quieting down, the temperature falling to normal, and the general health markedly improving. In December 1912 he began tuberculin treatment, and thus reports on it:

"My first injection, early in December, was 1/1,000,000th. T.R. This was worked up, in the usual manner, to 1/1,000th, given early in May. Here I had my first and last reaction, and my doctor put the dose back to 1/5,000th. I had nine doses of this last strength, and then, in July, left off the treatment. As to the effect of it, I must confess I am rather sceptical as to the value of tuberculin. I quite failed to detect the slightest effect either one way or the other. My doctor is very reluctant to give any opinion on the point, but states that there is nothing to show that my progress was affected either for good or ill by the tuberculin injections."

CASE 45

Mr. I. Age 40.

Type of case, moderately advanced disease (Group 2), with impaired digestion, and general condition unfavourable.

Discharged from the sanatorium December 1911, without material improvement.

Died March 1913.

A member of his family writes: "After leaving Midhurst he continued at work for exactly twelve months. During this time he had tuberculin, because he said he was not cured. However, at the end of about the seventeenth injection, his temperature rose considerably, and he gradually got worse."

The patient's medical attendant has kindly sent me the following notes: "The patient came to me in January 1912, and asked for tuberculin treatment. I told him from the first that his chance was a poor one. The first dose of .002 c.c. P.T.O. was increased twice a week, in the absence of reactions up to .5 c.c. P.T. in November. Up to September he seemed to keep *in statu quo*; after that, he began to go down hill with evidence of mixed infection, pleurisy, and digestive troubles. My personal opinion of the value of tuberculin is suspended until further evidence is available."

CASE 46

Mr. F. Age 33.

Type of case, moderately advanced disease (Group 2).

Discharged from the sanatorium March 1908. "Arrested." Quiescent disease at the apices of both lungs. General health excellent. Doing heavy work in the gardens a.m., and walking nine to ten miles daily. Above normal weight. Temperature normal. No sputum.

"After-history" returns for 1909-12, "Well and at work."

Report for 1913: "In November 1912 symptoms of the old trouble developed, but nothing could be found in the chest. On December 14th, the 28th, and again on January 20th, there was some haemoptysis. I resorted to strict sanatorium treatment, namely, feeding, rest, and graduated exercise. I regained my normal weight and was walking eight miles daily without the least fatigue, and with a perfectly normal temperature. At this point, a specialist was consulted, who recommended tuberculin. I protested, saying I was doing

extremely well. A scientific friend of mine made inquiries for me, and learnt that tuberculin in the present state of knowledge is dangerous. However, the specialist reassured my doctor, and I was persuaded to have the treatment. The tuberculin used was T.R. The following is the record of events :

1st dose, March 22nd	.	No rise of temp., some malaise.
2nd dose, March 29th	.	No rise of temp., some malaise.
3rd dose, April 5th	.	No effects.
4th dose, April 12th	.	Slight malaise.

"There was now an interval while we waited for instructions as to dosage from the specialist. I then went up to town, and was prescribed a course of increasing doses. At this time I was tremendously fit.

"The treatment proceeded as follows :

May 17th, 1/100,000	.	Slight malaise.
24th, 1/75,000	.	" "
31st, 1/50,000	.	Cough first began.
About June 1st	.	First had sputum.
June 7th, 1/40,000	.	Sputum was coloured.

"I reported this, but was advised to continue the inoculations.

June 14th, 1/30,000 . . . Coughed up a clot of blood.

"At this point I refused to have any more tuberculin.

"July 1st, had the first of a series of haemorrhages.

"Coughed up elastic fibres and tubercle bacilli (sputum report). Temperature rose to 104° F.

"I began to go wrong about May 29th, feeling out-of-sorts and tired. I complained of these symptoms at the time. I am now once more following strict sanatorium treatment ; my temperature has steadied down to normal, and my sputum has stopped. This last business, however, has shaken my confidence, and as a result of it I have lost my appointment."

CASE 47

Mr. A. Age 31.

Type of case, early disease (Group 1).

Discharged from the sanatorium October 1910.

"Much improved." Quiescent disease of the left apex. Temperature normal. Exercise: Work in the gardens and five miles walking. Up to weight; sputum traces, but containing bacilli.

His "after-history" return for 1912 was "Good health maintained."

On his "after-history" return for 1913, he writes as follows: "I began a course of tuberculin injections under my local doctor in October 1912, and finished in March 1913. There seemed to be a slight improvement until February, when I must have caught a chill."

In reply to a request for more detailed information, the patient writes as follows:

"1. The variety of tuberculin used was T.R.

"2. Doses.—1/50,000 milligramme, gradually increased to 1/5,000.

"3. Intervals.—Weekly from November 1912 to March 2nd, 1913.

"4. Reactions.—Hardly any at first, but after about the fifth injection there was a slight rise of temperature, but the rises had never been more than a degree above the ordinary level.

"5. As to the effect, I noticed a slight improvement as regards sputum during the earlier part of the course, but the set-back in February upset things altogether. My impression is that tuberculin is not so beneficial as sanatorium life. In my own case it was a case of open-air treatment plus tuberculin, as I was carrying out sanatorium treatment all the time.

"6. My present condition is fair, but my temperature has never settled down since the relapse in February."

CASE 48

Miss O. Age 33.

Type of case, moderately advanced disease (Group 2).

Discharged from the sanatorium April 1910.

"Much improved." Loss of resonance only at the apices of both lungs. General condition favourable. Sputum small amount, containing T.B.

Since leaving the sanatorium has followed the open-air treatment in the country, and maintained very fair health. With regard to tuberculin, the patient writes (October 1913): "I started tuberculin soon after I left Midhurst in 1910. I think it was old tuberculin. I continued with it for about a year, with very slight increases of dose, and with slight temperature reactions only with the larger doses. It did not seem to do me any good. I then left it off for six months and began again with B.E. This time I began with very small doses, and continued with very small increases of dose. As the injections became stronger, I had severe reactions, the temperature rising to 102° or 103°. I then went back again to small doses every four days, but I am now having reactions again, the last dose having been 2 c.c. B.E. My health remains very fair, and I have no sputum."

CASE 49

Miss X. Age 42.

Type of case, extensive chronic disease with much fibrosis (Group 3), with tuberculosis of larynx.

Discharged from the sanatorium April 1909. "Much improved." Condition favourable. Disease quiescent. Temperature normal. Walking six miles daily. T.B. absent from the sputum.

Readmitted January 1910, discharged May 1910. Lung disease arrested. Larynx well. General condition excellent. Sputum still clear of bacilli.

Since 1910 the patient has lived an open-air life in the country, and her "after-history" returns are as under:

1911. "Health as on leaving the sanatorium maintained."

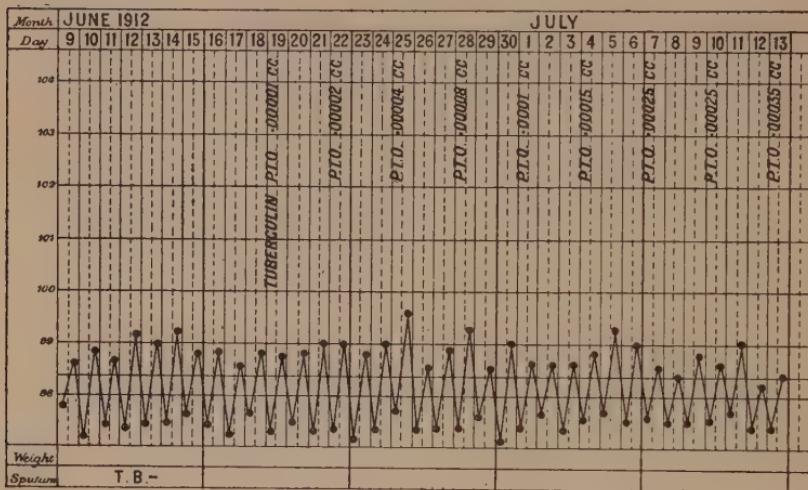
1912. "Enjoying very fair health."

1913. "Still in very fair health. Have had tuberculin."

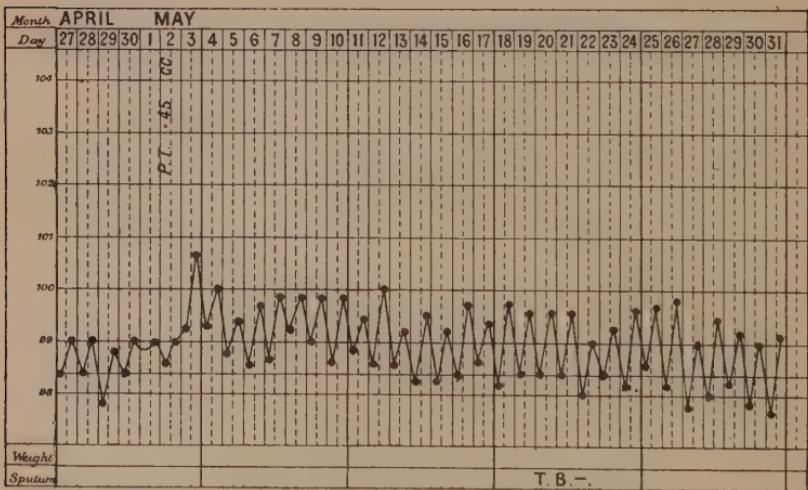
In an accompanying letter she writes: "I had tuberculin from June 1912 to May 1913, and enclose you my charts for this period, as they will interest you." (The charts record

124 PRELIMINARY REPORT ON TUBERCULIN

CHART 22.



1912, FIRST FIVE WEEKS OF TREATMENT.



1913, LAST FIVE WEEKS OF TREATMENT.

the usual sequence of doses throughout a course of P.T.O. and P.T., and six slight reactions. They also show that there was a gain of weight of 13 lb. during the period covered.

by treatment in a sanatorium with the addition of tuberculin, and that no tubercle bacilli were found in the sputum at any time. I have copied from these charts the records for the first five weeks, which cover a period of ten days before tuberculin was given, and the last five weeks, which include the date of the last inoculation.—N.D.B.) The letter continues: "I was unwell at the end of April 1912, and had lost 14 lb. in weight ; for this reason I went to the sanatorium in June. During the summer I was very well, and increased in weight. There were no bacilli in my sputum at any time. The early doses of tuberculin did not affect me at all. As time went on I generally felt slight reactions—as a rule what I would call an 'influenzaish' feeling on the day following the dose. Sometimes, too, I had a good deal of local reaction. After eight months' treatment I left the sanatorium and had the tuberculin sent to me by post. The last dose I had made me feel ill, and I had a tremendous local reaction. I injected myself, and therefore had to do it in the calf of the leg ; it was greatly swollen and quite black from my ankle to under my knee. I was then advised to leave off tuberculin, at least for a while. As to exercise : when I was having the tuberculin by post, my exercise was erratic, but throughout the treatment I was by way of keeping quiet for eighteen hours or more after an injection, so that tuberculin did affect my exercise a bit. I don't know whether the treatment can be said to have done me good or not, and I am doubtful whether I benefited. Bacilli were not found either before or after the inoculations, and I gather that the sounds in my lungs did not alter much. I was disappointed that the treatment did not take away my cough."

CASE 50

Mr. D. Age 28.

Type of case, early disease (Group 1).

Discharged February 1908. Condition, "much improved." Disease arrested, general health favourable. Temperature normal. Weight above normal. Exercise, heavy work in the grounds a.m. Six miles walking p.m. No T.B. to be

found in the sputum. (They were present on the patient's admission.)

Mr. D reported in his "after-history" return for 1913 that he had had a course of tuberculin with good results, and in answer to a request for further information kindly sent a detailed report, of which the following is an abstract. (Letter 1) "I am only too glad to give you any information that I can with regard to my course of tuberculin, because as a layman I feel strongly that a system that allows a patient to carry on with his ordinary work and to earn his own living during treatment must be better than residence in a sanatorium, especially to one like myself, to whom enforced rest is a continual source of worry.

" My history is as follows : I contracted the disease in 1907, and was admitted to the Midhurst Sanatorium in November of that year. I remained there until the end of February 1908, and then followed out the open-air treatment until the end of May. I returned to work, and continued in good health till July 1909. I then had a second breakdown, and again carried out sanatorium treatment in the country until December. At this date I was examined by a medical board, who pronounced me unfit for further service in the Navy. I went to Arosa in the following January (1910), and remained there until the end of March, returning to England in apparently good health. In the following October I obtained a post in a telegraph company. The work was fairly arduous, and carried out under somewhat unfavourable conditions for any one with arrested lung-disease. My condition gradually deteriorated, and in February 1911 I realised that I was very far from well. I was then advised to have a course of tuberculin. I began this treatment about the end of February, and within a few days had a somewhat severe haemorrhage. This was distinctly disappointing ; however, I was reassured, and continued the inoculations. In the first week of April I sailed for India. I continued the treatment from the date of leaving this country, but at a very much slower rate. My work in India was arduous ; I was in charge of four stations, 1,200 miles apart. I travelled 14,000 miles by rail in six months, working every day in the sun at a temperature which reached

116° in the shade. I spent the evenings in clerical work, and the nights in trying to get to sleep in spite of the heat. I was taking tuberculin regularly all the time ; it sometimes upset me for a bit, but my temperature never rose above 101°. I finished the treatment in March 1912, and arrived in England in the following June, thoroughly well. I have since been at work in a London office. Twelve months later, I began a series of tests. This test, so far as I can see, consists in taking one over the whole course of treatment at a much-increased rate, and in about six weeks the doses had attained the strength at which my previous treatment was stopped. I am still under the test, and so far the tuberculin has had very little effect.

"I am sorry that I cannot tell you whether I had bacilli in my sputum when I began the treatment, as I do not remember the sputum having been examined. As far as I can judge, the presence of bacilli is not of much importance in this particular treatment. Patients are tested to see if they are susceptible to tuberculosis ; if they are, they are treated so that they become no longer susceptible. One may be in normal health and yet just as much in need of this treatment as if one had advanced disease, because one's condition of health might be such that a very slight infection might produce most serious results. This treatment I think is primarily preventative in character, and secondarily curative. I do not think it claims to heal a damaged lung, but I may be wrong on this point. However, it improves one's constitution so that the tuberculous infection is eliminated from the damaged area, which then heals itself, the constitution at the same time being so strengthened that further infection is impossible. I would add that since starting this treatment, in February 1911, I have had no fear of another breakdown, although my work has been of a somewhat arduous character."

(Letter 2) "With regard to my condition when I began the treatment : I had a cough which was gradually getting worse, also a certain amount of fever, my morning temperature averaging about 97.8° and my evening temperature about 99.6°.

"As to the details of administration of tuberculin : I

left for India with eighteen doses, which were to be taken at intervals of three and four days, and I inoculated myself. I sent home by every mail a record of my temperature, and had a scale to work by, namely, if the temperature rose above 99.5° wait an additional day before having the next inoculation ; if above 100°, wait two additional days, and so on. When this first lot of doses were exhausted, relays were sent out, perhaps six at a time. They were all distinguished by means of a number, and the date on which they should be taken. My temperature rose above 99.5° after the majority of the inoculations, but my highest reaction was only 101°."

CASE 51

Mr. S. Aged 23.

Type of case, moderately advanced disease (Group 2).

Discharged March 1912. "Much improved." Condition favourable. Weight 6 lb. above normal weight. Temperature normal. Exercise, nine miles daily. Sputum, traces, containing bacilli.

In his "after-history" return for 1913, the patient writes : " After leaving Midhurst, eighteen months ago, I went to Bournemouth for two months, but the place was too relaxing for me, and I lost ground a little. On my return home in July I had an open-air shelter built in my garden, and have followed the sanatorium treatment ever since. At the same date I began tuberculin, and am still having it. In all, I have now had the injections for fourteen months, and although there is an improvement in my condition, it is not much considering the length of time I have been having tuberculin, and I am wondering whether it is worth while going on. My sputum still contains bacilli, and my weight has gone down a lot. As regards exercise, at the sanatorium I was doing nine miles a day with ease, and last winter I was doing about ten. Since this last summer, however, I have not felt up to this."

This patient was treated at a dispensary, and has kept very careful records. The inoculations were given in the evening, the patient remaining in bed for the next day. Tuberculin treatment began on July 11, 1912, with .00005 c.c. P.T.O., and

PRELIMINARY REPORT ON TUBERCULIN 129

on December 12th 1 c.c. of this preparation was given. This part of the course was uneventful except for the following : August 22nd, '0075 P.T.O. Evening temperature 100·2°, and for the four following days 100°. September 19th, temperature 100°.

A course of P.T. was begun on December 19th with '01 c.c., and finished on June 19th with '9 c.c. On December 24th following the injection of '02 c.c., the morning temperature was 100·6°, and the patient was confined to bed with headache. The record continues as follows :

Jan. 2nd and 3rd, in bed with headache. Jan. 17th, after '05 c.c., morning temperature 101·4°, afternoon temperature 100°. Jan. 31st, after '045 c.c. P.T., morning temperature 100·2°. June 20th, after '9 c.c. P.T., evening temperature 100·2°. A course of B.E. was begun on June 26th, with '005 c.c. On Sept. 3rd, after '035 c.c., the temperature rose to 100·2°. On Sept. 9th the patient was given a repeat dose of '035 c.c. On the following day, Sept. 10th, the evening temperature rose to 101·4°, and on the 11th it remained at 100·4°.

At this point the record ends.

In a letter dated a fortnight later the patient adds : " When I have a reaction, it makes my head ache very much, and puts me off my food, but a reaction seldom lasts beyond the second day after an inoculation. I have not done much walking since my weight started going down, and in consequence am rather soft in the muscles. I am not feeling very bright at present, and certainly have more cough and sputum than I had a month ago ; in fact, I have felt off colour throughout this past summer."

CASE 52

Miss P. Age 40.

Type of case, probably quiescent or arrested disease at the apices of both lungs. Discharged November 1909. No evidence of active disease, no sputum, no record of T.B. having been found at any time, either before or after admission. General health indifferent, of nervous constitution.

The patient reported annually as follows :

1910. "Health very fair."

1911. "Health very fair."

1912. "Health very fair."

1913. "Not quite so well. Have been having tuberculin for many months, and continue to live the sanatorium life."

In an accompanying letter she gives further particulars : "I started tuberculin about three months after I left the sanatorium, when I had an attack of tubercular peritonitis, starting with 1/50,000 milligramme of mixed human and bovine. I had this for nearly three months ; the doses were never much increased, and were sometimes mixed with a vaccine. After that I was in hospital for six months, and had tuberculin for about four months of that time. I then had it by the mouth, and since then have continued having it this way, as I find it answers just as well as the injections. I have dropped it from time to time, but always seem to go back after a short time without it. My doctor says he thinks it does me more good than anything else. With the larger doses there is sometimes a reaction in temperature, with slight headache. My last dose was 1/5,000 milligramme T.R. With regard to my sputum, so far as I know no one has ever found bacilli."

CASE 53

Mrs. Y. Age 30.

Type of case, moderately advanced disease (Group 2). Discharged February 1910, "much improved." General condition favourable. Up to normal weight. Afebrile. Exercise five miles daily. T.B. in the sputum.

Died February 1911.

A relative of this patient reported her death in the following words : "She never seemed so well as whilst in the sanatorium, and a few months after leaving she had an attack of pleurisy. She then went to the seaside, and returned much better. At this date she began tuberculin treatment, the injections being given twice a week. For the first few months she seemed much better, in all probability the effect of her faith in the treatment. The earlier strengths of the injections

PRELIMINARY REPORT ON TUBERCULIN 131

had no ill effects, but the latter ones played havoc with her. They affected her temperature, and she suffered awfully with headache, and was often delirious after an injection. After twelve months of this treatment, the disease spread to other parts of her body, and she steadily lost ground."

I am indebted to the patient's physician for the following notes: "She took tuberculin well at first with hardly any reactions, but lost a few pounds in weight. Later she suddenly reacted to 102·6°, but the next two doses only slightly affected her. On subsequent doses, she again reacted to 103°, 102°, and 103°. The doses were then reduced, and the intervals between the doses lengthened. After this she went on fairly well for two or three weeks, but then again reacted to 101·6°. I then tried another form of tuberculin, but as the weight continued to fall, I gave it up altogether. The steady fall in weight was discouraging, but I have seen improvement and recovery take place during tuberculin treatment, even when patients have lost a stone; I therefore continued the treatment in the hope that this particular patient might have this good fortune."

SECTION XXI

Summary of the Experience gained at Midhurst, up to October 1913, in the Treatment of Pulmonary Tuberculosis with Tuberculin

It is impossible to give anything like a final opinion as to the value of tuberculin on the strength of our present experience. Further data are necessary, especially those to be obtained from the subsequent life-histories of our patients who have been treated with tuberculin, and our observations have been necessarily limited to the results of tuberculin when administered by the method described earlier in this report (see p. 11 *et seq.*) ; which, as it is the one in most general use, was first selected for trial. However, after eighteen months' work with tuberculin, some expression of opinion as to its value may reasonably be expected, even if it be no more than a suggestion as to the direction in which that opinion is tending.

Experience has shown that tuberculin, as at present used, is not a remedial agent which can be depended upon to revolutionise either our sanatorium results or our conception of the outlook for the average consumptive. Tuberculin has not proved itself to be a remedy in the ordinary sense of the term, and no immediate or striking results are to be expected from it, even in the most favourable cases. Even if it be assumed that good effects are produced by tuberculin, they occur almost imperceptibly, the slowness of its action being such that it is often difficult to determine, as regards patients treated under favourable hygienic conditions, how much if any of the improvement that takes place is due to its use.

Tuberculin, as employed in this sanatorium during the period covered by this report, in association with the favourable conditions which are secured by residence in the institution, exercises an influence in those cases in which steadily increasing doses can be taken. The treatment produces (1) tolerance to considerable doses of tuberculin and, in many cases, (2) an effect on the diseased structures. This local effect may be a source of danger.

As to the kind of case in which it may be expected that tuberculin treatment is at least without unfavourable effect, our experience is that it is the patient with a good outlook, who has rapidly responded to general hygienic measures, and who has shown evidence of constitutional vigour and recuperative power.

In a considerable number of cases tuberculin, so far as can be judged from immediate clinical results, has no obvious influence on the lesions. The patient is gradually made tolerant to it, but this seems to be the only objective indication of its effect. Whether this tolerance is of value is at present a matter of uncertainty. Further, in a proportion of cases, tuberculin is not merely inert ; it is definitely prejudicial.

As far as the Midhurst results show, tuberculin cannot be looked upon as a means whereby an unfavourable case can be converted into a favourable one, or as likely to turn the scale in a patient's favour, when his progress is doubtful, and certainly not when it is definitely retrogressive. More often than not in such cases it will do harm.

Our experience up to the present time shows that the administration of tuberculin is quite unsuitable as a routine method of treatment for all cases of pulmonary tuberculosis, and that its indiscriminate and careless use on a large scale can only end in harm.

APPENDIX I

CASES IN WHICH, ON ADMISSION AND THROUGHOUT TREATMENT, T.B. WERE NOT FOUND IN THE SPUTUM. THESE CASES, NOT TESTED WITH TUBERCULIN FOR VARIOUS REASONS, HAD SIGNS OR SYMPTOMS VERY STRONGLY SUGGESTIVE OF RECENTLY ACTIVE PULMONARY TUBERCULOSIS, AND WERE TREATED AS SUCH

Febrile or Afebrile.	On Admission.						On Discharge.			
	Relation of Weight to Normal Weight.	Length of Treatment in Weeks.	Length of Tuberculin Treatment in Weeks.	Variety of Tuberculin Used.	No. of Inocula- tions.	Condition of Lungs.	Daily Exercise in Miles.	Relation of Weight to Normal Weight.	Maximum Tuberculin Dose. c.c.	
Afebrile .	±	22	20	A.F.	22	Much improved	5	+ 16 lb.	.003 ¹	
do. .	— 9 lb.	20	12	A.F.	20	Unaltered	7	+ 14 lb.	.07	
do. .	— 4 lb.	13	10	A.F.	18	Improved	6	+ 10 lb.	.004 ²	
do. .	— 2 lb.	12	8	A.F.	15	Nil definite	6	— 2 lb.	.001	
do. .	— 20 lb.	24	20	A.F.	27	Unaltered	9	— 9 lb.	.008 ³	
do. .	±	12	8	A.F.	12	Nil definite	5	±	.0003	
Febrile .	— 8 lb.	30	12	A.F.	17	Improved	8	— 4 lb.	.015	
Afebrile .	— 2 lb.	11	6	A.F.	9	Unaltered	8	+ 11 lb.	.0005 ³	
Febrile (L)	±	34	18	A.F.	23	Much improved	12	±	.5	
Afebrile .	— 9 lb.	15	10	A.F.	10	Nil definite	6	±	.015	
do. .	— 10 lb.	22	10	A.F.	7	do.	6	— 5 lb.	.01	
do. .	— 10 lb.	22	15	A.F.	24	Unaltered	10	— 10 lb.	.5	
do. .	+ 8 lb.	32	21	A.F.	28	do.	6	+ 12 lb.	.5 ⁴	

(L) Indicates that the patient had tuberculosis of larynx.

¹ 20 years' history of Pulmonary Tuberculosis; T.B. repeatedly found.

² T.B. found 4 weeks before admission, but not subsequently.

³ Recent haemoptysis.

⁴ T.B. found 2½ years before admission, but not since.

APPENDIX II

CASES IN WHICH, ON ADMISSION AND THROUGHOUT TREATMENT, T.B. WERE NOT FOUND IN THE SPUTUM, BUT WHICH GAVE A FOCAL REACTION TO DIAGNOSTIC DOSES OF TUBERCULIN

Febrile or Afebrile.	On Admission.					On Discharge.				
	Relation of Weight to Normal Weight.	Length of Treatment in Weeks.	Length of Tuberculin Treatment in Weeks.	Variety of Tuberculin Used.	No. of Inocula- tions.	Condition of Lungs.	Daily Exercise in Miles.	Relation of Weight to Normal Weight.	Maximum Tuberculin Dose. c.c.	
Afebrile .	+	16	9	A.F.	13	Unaltered	6	+	.005	
do. .	++	21	16	A.F.	19	do.	10	+ 14 lb.	.03	
do. .	++	31	20	A.F.	28	do.	8	+ 3 lb.	.7	
do. .	++	18	10	A.F.	14	do.	12	+ 14 lb.	.15	
do. .	++	31	23	A.F.	30	do.	10	+ 17 lb.	.15	
do. .	— 4 lb.	37	34	A.F.	39	do.	10	+ 5 lb.	1 c.c.	
Febrile .	— 11 lb.	32	27	B.E.	32	do.	6	+	.001	
do. .	— 13 lb.	36	23	B.E.	36	do.	6	+ 8 lb.	.00007	
Afebrile (L)	±	24	17	A.F.	18	Larynx improved	10	+ 18 lb.	.07	
Afebrile .	— 8 lb.	22	16	A.F.	18	Unaltered	6	+ 3 lb.	.065	
Febrile .	— 4 lb.	20	13	A.F.	18	do.	6	+ 6 lb.	.01	

(L) Indicates that the patient had tuberculosis of larynx.

APPENDIX III

CASES IN WHICH, ON ADMISSION TO THE SANATORIUM, T.B. WERE FOUND IN THE SPUTUM

GROUP I¹

Afebrile or Febrile.	On Admission.					On Discharge.				
	Relation of Weight to Normal Weight.	Length of Treatment in Weeks.	Length of Tuberculin Treatment in Weeks.	Variety of Tuberculin Used.	No. of Inocula- tions.	Condition of Lungs.	Daily Exercise in Miles.	Relation of Weight to Normal Weight.	T.B. + or -.	
Afebrile .	+	4 lb.	15	12	A.F.	18	Much improved	+ 10 lb.	-	
do. .	-	4 lb.	19	16	A.F.	23	do.	+ 14 lb.	-	
do. .	-	9 lb.	29	27	B.E.	27	do.	+ 14 lb.	-	
do. .	+				A.F.					
Febrile .	-	4 lb.	17	14	A.F.	20	do.	+ 8 lb.	-	
do. .	-	14 lb.	20	9	A.F.	9	do.	+ 12 lb.	-	
Afebrile .	-	5 lb.	17	14	A.F.	20	Unaltered	- 14 lb.	-	
do. .	+	11 lb.	8	3	T.R.	3	Much improved	+ .8 lb.	+	
do. .	+	12 lb.	12	8	A.F.	12	do.	+ 17 lb.	+	
do. .	+	6 lb.	35	31	A.F.	44	do.	+ 13 lb.	-	
do. .	+				B.E.		Much improved			
do. .	+				A.F.	23	do.	+ 16 lb.	+	
do. .	+				B.E.		do.		-	
do. .	-	3 lb.	38	25	A.F.	35	do.	+ 16 lb.	-	
do. .	+	25 lb.	45	42	B.E.		do.		-	
do. .	+				T.R.	45	do.	+ 27 lb.	-	
do. .	+				A.F.		do.		-	
do. .	+				A.F.	30	do.	+ 4 lb.	+	
do. .	+				A.F.	34	do.	±	-	
do. .	+				B.E.		do.		-	
do. .	-	5 lb.	8	4	A.F.	8	do.	+ 10 lb.	-	
do. .	+				B.E.	16	do.	+ 9 lb.	-	
do. .	+				B.E.	13	do.	+ 3 lb.	-	
do. .	+				B.E.	15	do.	+ 9 lb.	-	
do. .	+				A.F.	19	do.	±	-	
do. .	+				B.E.		do.		-	
Febrile .	++		10	5	A.F.	6	do.	+ 6 lb.	-	
Afebrile .	++		24	20	A.F.	24	do.	+ 14 lb.	-	

(L) Indicates that the patient had tuberculosis of larynx.

¹ For definition of Groups, see page 68.

APPENDIX IV

CASES IN WHICH, ON ADMISSION TO THE SANATORIUM, T.B. WERE FOUND IN THE SPUTUM

GROUP II

Afebrile or Febrile.	On Admission.					On Discharge.					T.B. + or -
	Relation of Weight to Normal Weight.	Length of Treatment in Weeks.	Length of Tuberculin Treatment in Weeks.	Variety of Tuberculin Used.	No. of Inocula- tions.	Condition of Lungs.	Daily Exercise in Miles.	Relation of Weight to Normal Weight.			
Febrile .	- 14 lb.	24	10	A.F.	18	Much improved	12	+	5 lb.	-	
do. .	- 32 lb.	22	9	A.F. B.E.	13	Unaltered	1	-	30 lb.	+	
do. .	- 7 lb.	12	3	A.F.	3	do.	1	±		+	
Afebrile .	+ 8 lb.	15	12	A.F.	16	Much improved	6	+	15 lb.	+	
Febrile .	±	21	12	A.F.	19	do.	6	+	5 lb.	+	
Afebrile .	±	8	7	B.E.	12	Improved	6	+	7 lb.	+	
do. .	- 8 lb.	21	19	A.F.	29	Much improved	12	-	2 lb.	-	
do. .	±	15	13	A.F.	21	do.	8	+	20 lb.	-	
do. .	±	13	8	A.F.	12	do.	10	+	4 lb.	-	
do. .	±	12	7	A.F.	15	Unaltered	5	+	2 lb.	+	
do. .	- 10 lb.	19	15	A.F.	15	Much improved	6	-	3 lb.	-	
Febrile (L)	±	18	2	A.F.	5	Unaltered	nil	+	7 lb.	+	
do. (L)	±	43	32	A.F.	44	Much improved	8	+	18 lb.	-	
do. (L)	+ 5 lb.	38	17	B.E.	17	Worse	Nil	±		+	
do. (L)	- 8 lb.	29	20	B.E.	22	Improved	6	+	4 lb.	+	
do. (L)	- 7 lb.	12	6	A.F.	7	Unaltered	Nil	+	4 lb.	+	
Febrile (L)	- 10 lb.	16	7	A.F.	6	do.	Nil	±		+	
do. (L)	- 3 lb.	7	3	A.F.	3	Improved	2	+	5 lb.	+	
Afebrile(L)	±	41	36	T.R.	37	Much improved	6	-	6 lb.	+	
Febrile (L)	±	14	6	A.F.	13	Unaltered	4	-	6 lb.	+	
do. (L)	+ 14 lb.	40	21	A.F. B.E.	24	Improved	6	+	4 lb.	+	
Febrile .	- 11 lb.	42	29	A.F. B.E.	37	Much improved	10	-	6 lb.	-	
Afebrile .	- 12 lb.	36	28	A.F. B.E.	37	do.	10	-	6 lb.	+	
Febrile .	- 6 lb.	34	25	A.F.	31	do.	10	+	17 lb.	+	
Afebrile .	±	32	29	A.F. B.E.	32	do.	6	+	6 lb.	+	
Febrile .	±	31	3	B.E.	6	Much improved	10	+	12 lb.	+	
Afebrile .	- 8 lb.	33	31	A.F. B.E.	41	do.	6	-	2 lb.	+	
Febrile .	- 23 lb.	33	11	A.F.	14	do.	5	-	9 lb.	+	
Febrile (L)	- 3 lb.	13	10	A.F.	15	do.	10	+	4 lb.	-	
Afebrile .	±	15	13	A.F.	19	do.	10	+	7 lb.	+	
do. .	±	30	27	A.F. B.E.	40	do.	10	±		+	

(L) Indicates that the patient had tuberculosis of larynx.

APPENDIX IV (*continued*)

GROUP II (*continued*)

Afebrile or Febrile.	On Admission.						On Discharge.				T.B. + or -
	Relation of Weight to Normal Weight.	Length of Treatment in Weeks.	Length of Tuberculin Treatment in Weeks.	Variety of Tuberculin Used.	No. of Inocula- tions.	Condition of Lungs.	Daily Exercise in Miles.	Relation of Weight to Normal Weight.			
Afebrile	- 2 lb.	36	7	T.R.	11	Much improved	4	+ 11 lb.		+	
do.	- 10 lb.	27	3	A.F.	5	do.	8	+ 7 lb.		-	
Febrile	- 18 lb.	30	18	B.E.	20	do.	6	+ 1		-	
do.	- 14 lb.	32	16	A.F.	25	do.	10	- 5 lb.		-	
Afebrile	±	7	5	B.E.	8	do.	4	+ 3 lb.		-	
do.	- 24 lb.	25	20	A.F.	27	Unaltered	1	±		+	
do.	±	57	45	A.F.	51	Improved	6	+ 10 lb.		+	
				B.E.							
do.	- 10 lb.	19	18	B.E.	26	Much improved	8	+ 9 lb.		-	
do.	±	17	14	A.F.	21	do.	8	+ 11 lb.		-	
Febrile	±	40	26	A.F.	37	do.	10	+ 4 lb.		-	
				B.E.							
Afebrile	+ 28 lb.	26	13	A.F.	16	do.	8	+ 25 lb.		+	
do.	+ 9 lb.	44	26	T.R.	36	do.	8	+ 9 lb.		+	
				A.F.							
Febrile	- 13 lb.	25	14	B.E.	15	Worse	Nil	- 9 lb.		+	
				A.F.							
do.	- 16 lb.	36	24	A.F.	32	Much improved	8	±		+	
				B.E.							
Febrile (L)	±	13	10	B.E.	20	Improved	3	+ 3 lb.		+	
Afebrile (L)	- 15 lb.	12	9	B.E.	12	Much improved	6	- 4 lb.		+	
Afebrile	- 11 lb.	23	19	A.F.	26	do.	10	- 5 lb.		+	
Febrile (L)	- 12 lb.	62	42	A.F.	56	do.	4	- 3 lb.		-	
				B.E.							
Afebrile	+ 14 lb.	6	4	A.F.	8	do.	12	+ 19 lb.		+	
do.	- 10 lb.	21	17	B.E.	25	do.	12	±		+	
do.	±	20	15	B.E.	19	do.	6	+ 13 lb.		+	
Febrile (L)	- 4 lb.	36	32	A.F.	44	do.	5	+ 15 lb.		+	
				B.E.							
Febrile	- 5 lb.	53	31	A.F.	45	do.	8	±		+	
				B.E.							
do.	±	54	32	A.F.	38	Worse	Nil	- 8 lb.		+	
Afebrile	- 2 lb.	20	14	A.F.	19	Much improved	10	+ 22 lb.		-	
						do.	10	+ 13 lb.		+	
do.	±	32	29	A.F.	32						
				B.E.							
do.	- 3 lb.	30	25	A.F.	38	do.	8	+ 11 lb.		-	
				B.E.							
do.	±	34	32	A.F.	40	do.	6	+ 11 lb.		+	
				B.E.							
do.	+ 10 lb.	32	28	A.F.	42	do.	12	+ 21 lb.		-	
				B.E.							
Afebrile (L)	±	16	10	B.E.	15	Improved	10	+ 9 lb.		+	
Febrile	- 7 lb.	36	13	B.E.	21	Much improved	8	+ 14 lb.		-	

(L) Indicates that the patient had tuberculosis of larynx.

APPENDIX IV (*continued*)

GROUP II. (*continued*)

Afebrile or Febrile.	On Admission.					On Discharge.				
	Relation of Weight to Normal Weight.	Length of Treatment in Weeks.	Length of Tuberculin Treatment in Weeks.	Variety of Tuberculin Used.	No. of Inocula- tions.	Condition of Lungs.	Daily Exercise in Miles.	Relation of Weight to Normal Weight.	T.B. + or -	
Afebrile . .	- 20 lb.	34	30	B.E.	24	Much improved.	10	±	-	
Febrile . .	±	39	30	A.F. B.E.	31	do.	8	+ 19 lb	+	
Afebrile . .	- 2 lb.	31	23	A.F. B.E.	28	do.	10	+ 7 lb.	-	
do. . .	- 4 lb.	36	28	B.E. A.F.	33	do.	10	+ 10 lb.	+	
do. . .	- 17 lb.	22	15	B.E.	15	do.	10	- 6 lb.	-	
do. . .	- 7 lb.	16	10	A.F.	17	Improved	7	+ 5 lb.	+	
do. . .	- 24 lb.	20	7	B.E.	9	Unaltered	2	- 9 lb.	+	
Afebrile (L)	- 7 lb.	24	12	B.E.	16	Improved	4	- 8 lb.	+	
Afebrile . .	+ 2 lb.	44	35	A.F. B.E.	46	Much improved	10	+ 14 lb.	+	
do. . .	- 7 lb.	36	33	A.F. B.E.	39	do.	6	+ 6 lb.	-	
do. . .	- 6 lb.	24	17	A.F.	25	do.	10	+ 17 lb.	-	
Febrile (L)	±	45	30	T.O. T.R.	32	do.	3	- 7 lb.	+	
Afebrile . .	+ 25 lb.	85	57	A.F. B.E.	57	do.	5	+ 17 lb.	+	
do. . .	- 14 lb.	32	29	A.F. B.E.	37	do.	10	+ 2 lb.	-	
do. . .	±	19	18	A.F.	24	do.	12	+ 2 lb.	+	
do. . .	- 8 lb.	34	33	A.F. B.E.	42	do.	6	- 2 lb.	+	
do. . .	+ 3 lb.	86	47	A.F. B.E.	62	do.	6	+ 9 lb.	+	
do. . .	- 14 lb.	68	46	A.F. B.E.	57	do.	9	- 10 lb.	-	
do. . .	+ 9 lb.	21	18	A.F.	25	Worse	6	+ 22 lb.	+	

(L) Indicates that the patient had tuberculosis of larynx.

APPENDIX V

CASES IN WHICH ON ADMISSION T.B. WERE FOUND IN THE SPUTUM

GROUP III

Afebrile or Febrile.	On Admission.					On Discharge.				T.B. + or -
	Relation of Weight to Normal Weight.	Length of Treatment in Weeks.	Length of Tuberculin Treatment in Weeks.	Variety of Tuberculin Used.	No. of Inocula- tions.	Condition of Lungs.	Daily Exercise in Miles.	Relation of Weight to Normal Weight.		
Febrile .	+	3 lb.	40	25	B.E.	28	Improved	3	+	2 lb.
Afebrile .	-	4 lb.	42	34	B.E.	43	Much improved	10	+	3 lb.
Febrile .	+	7 lb.	34	9	A.F. B.E.	15	Unaltered	5	-	5 lb.
Febrile (L)	-	12 lb.	24	9	A.F.	13	Improved	Nil	±	+
Febrile .	-	7 lb.	25	11	A.F. B.E.	14	do.	2	+	7 lb.
Febrile (L)	-	12 lb.	36	23	B.E.	22	Worse	Nil	-	5 lb.
Febrile .	-	9 lb.	25	5	A.F.	5	Unaltered	Nil	-	11 lb.
Afebrile .	-	7 lb.	30	24	A.F. B.E.	34	Much improved	7	+	6 lb.
Febrile (L)	-	6 lb.	17	5	A.F.	7	Worse	Nil	-	23 lb.
Afebrile .	-	6 lb.	28	17	A.F.	25	Much improved	4	±	+
Febrile .	-	10 lb.	13	8	A.F.	13	Improved	6	-	13 lb.
do. .	-	21 lb.	33	16	B.E.	18	Unaltered	Nil	-	26 lb.
Afebrile .	-	3 lb.	12	9	B.E.	15	Improved	7	+	6 lb.
Febrile .	±	22	18	B.E. A.F.	22	Unaltered	4	+	7 lb.	+
Afebrile .	-	2 lb.	12	8	A.F.	12	Improved	6	-	2 lb.
do. .	+	7 lb.	11	9	A.F.	14	do.	4	+	9 lb.
Febrile (L)	+	2 lb.	29	27	B.E.	18	do.	4	+	4 lb.
do. (L)	±	33	26	B.E. A.F.	31	do.	6	+	20 lb.	+
Afebrile (L)	-	23 lb.	11	8	A.F.	12	Unaltered	4	-	14 lb.
Febrile (L)	-	14 lb.	19	16	A.F.	20	Improved	6	±	+
do. (L)	-	8 lb.	25	19	A.F.	24	Unaltered	Nil	-	15 lb.
Febrile .	-	24 lb.	20	7	A.F.	9	do.	Nil	-	13 lb.
do. .	-	7 lb.	36	16	A.F.	22	Worse	Nil	-	23 lb.
do. .	-	21 lb.	28	16	B.E. S.B.E.	24	Unaltered	Nil	-	9 lb.
Afebrile .	-	4 lb.	53	51	A.F. B.E.	54	Much improved	6	+	12 lb.
do. .	±	40	28	A.F.	35	do.	10	+	17 lb.	-
Febrile .	±	36	20	B.E.	26	Improved	1	-	4 lb.	+

(L) Indicates that the patient had tuberculosis of larynx.

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